spousal smoking is shown in Figure 2 of Wald et al. (1986). A similar example is in Table 12-5 of the NRC report.

Both Lee's and Wald's work adjust an overall relative risk estimate, pooled over several studies, downward, rather than address each individual study, with its own peculiarities, separately. Furthermore, statistical analysis over the studies as a whole is conducted first, and then an adjustment is made to the overall relative risk estimate. The recent work of Wells and Stewart (Appendix B) on this subject makes an adjustment to each individual study separately. Consequently, the pertinent adjustment factors that vary by study and type of society can be tailored to each study and then applied to the observed data before any statistical analysis. The latter procedure is applied in this report.

The methodology to adjust for bias due to smoker misclassification and the details of its application to the ETS studies are provided in Appendix B. The results of the adjustment and estimate of bias are given in Table 5-8. In general, the biases are low in East Asia, or in any traditional society such as Greece, where female smoking prevalence is low and the female smoker risk is low. Some of the calculated biases are slightly less than unity when carried to three decimal places. This may result from the assumption in the calculations that there is no passive smoking effect on current smokers.

5.3. STATISTICAL INFERENCE

5.3.1. Introduction

Table 5-9 lists the values of several statistical measures for the effect of spousal smoking by study (see boldface entries in Table 5-6 for details). Their meanings will be described before proceeding to interpretation of the data, even though the concepts discussed may be familiar to most readers. The p-values refer to a test for effect and a test for trend. In the former, the null hypothesis of no association (referred to as "no effect" of ETS exposure on lung cancer risk) is tested against the alternative of a positive association. The test for trend applies to a null hypothesis of no association between RR and exposure level against the alternative of a positive association. When data are available on more than two levels of intensity or duration of ETS exposure, typically in terms of the husband's smoking habit (e.g., cig./day or years of smoking), then a test for trend is a useful supplement in testing for an effect, as well as indicating whether a dose-response relationship is likely.

The entries under "power" in Table 5-9 are calculated for the study's ability to detect a true relative risk of 1.5 and a decision rule to reject the null hypothesis of no effect when $p < 0.05$ (see Dupont and Plummer [1990] for methods to calculate power). The power is the estimated probability that the null hypothesis would be rejected if the true relative risk is 1.5 (i.e., that the

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Table 5-8. Estimated correction for smoker misclassification

Case control[1]	Never-smokers RR[1] Uncorrected[2] (1)		Corrected[3] (2)	Bias[4] (1)/(2)	Ever-smokers OR used[5]
AKIB	———	1.5 (1.0, 2.5)	———	1.00	2.38
BROW	1.52 (0.49, 4.79)		1.50 (0.48, 4.72)	1.01	4.30
BUFF	0.81 (0.39, 1.66)		0.68 (0.32, 1.41)	1.20	7.06
CHAN	0.75 (0.48, 1.19)		0.74 (0.47, 1.17)	1.01	3.48
CORR	2.07 (0.94, 4.52)		1.89 (0.85, 4.14)	1.10	12.40
FONT	1.29 (1.03, 1.62)		1.28 (1.03, 1.60)	1.01	8.0
GAO	———	1.19 (0.87, 1.63)	———	1.00	2.54
GARF	1.31 (0.93, 1.85)		1.27 (0.91, 1.79)	1.03	6.0
GENG	———	2.16 (1.21, 3.84)	———	1.00 (0.995)	2.77
HIRA	1.53 (1.10, 2.13)		1.52 (1.10, 2.12)	1.01	3.20
HUMB	2.2 (0.9, 5.5)		2.00 (0.83, 4.97)	1.10	16.3
INOU	———	2.55 (0.90, 7.20)	———	1.00 (0.996)	1.66
JANE	0.86 (0.57, 1.29)		0.79 (0.52, 1.17)	1.09	8.0
KABA	0.79 (0.30, 2.04)		0.73 (0.27, 1.89)	1.08	5.90
KALA	———	1.92 (1.13, 3.23)	———	1.00	3.32
KATA	*		*	*	*
KOO	1.55 (0.98, 2.44)		1.54 (0.98, 2.43)	1.01	2.77
LAMT	1.65 (1.21, 2.21)		1.64 (1.21, 2.21)	1.01	3.77

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Table 5-8. (continued)

Case control	Never-smokers RR[1] Uncorrected[2] (1)		Corrected[3] (2)	Bias[4] (1)/(2)	Ever-smokers OR used[5]
LAMW	———	2.51 (1.49, 4.23)	———	1.00 (0.996)	4.12
LEE	1.03 (0.48, 2.20)		1.01 (0.47, 2.15)	1.02	4.61
LIU	———	0.77 (0.35, 1.68)	———	1.00	*
PERS	1.2 (0.7, 2.1)[6]		1.17 (0.75, 1.87)	1.03	4.2
SHIM	1.08 (0.70, 1.68)		1.07 (0.7, 1.67)	1.01	2.8
SOBU	———	1.57 (1.13, 2.15)	———	1.00	2.81
SVEN	1.26 (0.65, 2.48)		1.20 (0.63, 2.36)	1.05	6.00
TRIC	———	2.08 (1.31, 3.29)	———	1.00	2.81
WU	1.41 (0.63, 3.15)		1.32 (0.59, 2.93)	1.07	4.38
WUWI	0.79 (0.64, 0.98)		0.78 (0.63, 0.96)	1.01	2.24
BUTL (Coh)	2.02[7] (0.48, 8.56)[6]		2.01 (0.61, 6.73)	1.00	4.0
GARF (Coh)	1.17[7] (0.85, 1.61)[6]		1.16 (0.89, 1.52)	1.01	3.58
HIRA (Coh)	1.38 (1.03, 1.87)		1.37 (1.02, 1.86)	1.01	3.20
HOLE (Coh)	1.99[7] (0.24, 16.7)[6]		1.97 (0.34, 11.67)	1.01	4.2

[1]OR for case-control studies; RR for cohort studies.
[2]Adjusted OR in Table 5-5 is used unless the confidence interval is unknown or the study review (Appendix A) is critical of the method(s) used.
[3]Corrected (2) (estimate and confidence interval) equals uncorrected (1) times ratio [(2)/(1)]. All corrected 95% confidence intervals have been converted to 90% confidence intervals.
[4]Values shown are the lower of (calculated ratio, 1). Calculated ratios less than 1 are shown in parentheses.
[5]The crude OR for ever-smokers in Table 5-5 is used in the calculations for the corrected value (Appendix B), when available. Ever-smoker ORs for GARF, JANE, PERS, and SHIM are approximated from the data of other studies for suitable location and time period. The ever-smoker ORs for BUTL(Coh) and (LEE) are based on data in Fraser et al. (1991) and Alderson et al. (1985), respectively.
[6]95% confidence interval.
[7]Adjusted RR value in Table 5-5.

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Table 5-9. Statistical measures by individual study and pooled by country, corrected for smoker misclassification[1]

Location	Study	Relative weight[2] (%)	Power[3]	P-value Effect[4]	P-value Trend[5]	RR[6]	Confidence interval 90%
Greece	KALA	43	0.39	0.02	0.04	1.92	(1.13, 3.23)
Greece	TRIC	57	0.45	<0.01	<0.01	2.08	(1.31, 3.29)
Greece	ALL	5		<0.01		2.01	(1.42, 2.84)
HK	CHAN	20	0.43	>0.5	*	0.74	(0.47, 1.17)
HK	KOO	20	0.43	0.06	0.16	1.54	(0.98, 2.43)
HK	LAMT	45	0.73	<0.01	<0.01	1.64	(1.21, 2.21)
HK	LAMW	15	0.39	<0.01	*	2.51	(1.49, 4.23)
HK	ALL	14		<0.01		1.48	(1.21, 1.81)
Japan	AKIB	15	0.42	0.05	0.03	1.50	(1.00, 2.50)
Japan	HIRA (Coh)	35	0.75	0.04	<0.01	1.37	(1.02, 1.86)
Japan	INOU	3	0.17	0.07	<0.03	2.55	(0.90, 7.20)
Japan	SHIM	16	0.37[7]	0.38	*	1.07	(0.70, 1.67)
Japan	SOBU	30	0.66	0.01	*	1.57	(1.13, 2.15)
Japan	ALL	19		<0.01		1.41	(1.18, 1.69)
USA	BROW	1	0.15	0.28	*	1.50	(0.48, 4.72)
USA	BUFF	3	0.17	>0.5	*	0.68	(0.32, 1.41)
USA	BUTL (Coh)	1	0.18	0.17	*	2.01	(0.61, 6.73)
USA	CORR	3	0.22	0.10	0.01	1.89	(0.85, 4.14)
USA	FONT[8]	35	0.93	0.03	0.04	1.28	(1.03, 1.60)
USA	GARF	15	0.60[7]	0.12	<0.02	1.27	(0.91, 1.79)

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Table 5-9. (continued)

Location	Study	Relative weight[2] (%)	Power[3]	P-value Effect[4]	P-value Trend[5]	RR[6]	Confidence interval 90%
USA	GARF (Coh)	25	0.92	0.18	*	1.16	(0.89, 1.52)
USA	HUMB	2	0.20	0.10	*	2.00	(0.83, 4.97)
USA	JANE	10	0.44[7]	>0.5	*	0.79	(0.52, 1.17)
USA	KABA	2	0.17[7]	>0.5	*	0.73	(0.27, 1.89)
USA	WU	3	0.21	0.29	*	1.32	(0.59, 2.93)
USA	ALL	34		0.02		1.19	(1.04, 1.35)
Scotland	HOLE (Coh)	100	0.09	0.26	*	1.97	(0.34, 11.67)
Eng./Wales	LEE	100	0.20	0.50	*	1.01	(0.47, 2.15)
Sweden	PERS	68	0.45[7]	0.27	0.12	1.17	(0.75, 1.87)
Sweden	SVEN	32	0.24	0.31	*	1.20	(0.63, 2.36)
W. Europe	ALL	5		0.22		1.17	(0.84, 1.62)
China	GAO	28	0.66	0.18	0.29	1.19	(0.87, 1.62)
China	GENG	8	0.32	0.01	<0.05	2.16	(1.21, 3.84)
China	LIU	4	0.18	>0.5	*	0.77	(0.35, 1.68)
China	WUWI	60	0.89[7]	>0.5	*	0.78	(0.63, 0.96)
China	ALL	22		>0.5		0.95	(0.81, 1.12)

[1]Misclassification is discussed in Section 5.2.2 and Appendix B.
[2]A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3]*A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4]One-sided p-value for test of RR = 1 versus RR > 1.
[5]P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative, i.e., upward trend.
[6]Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[7]Calculated for matched study design.
[8]For population control group only, all cases.

*Data not available; ns = not significant.

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correct decision would result; the power would be larger if the true relative risk exceeds 1.5). If the estimates of power for the U.S. studies in Table 5-9 are used for illustration, it can be seen that the estimated probability that a study would *fail* to detect a true relative risk of 1.5 (equal to 1 – Power, the probability of a Type II error [discussed in the next paragraph] when the true relative risk is 1.5) is as follows: FONT, 0.07; GARF(Coh), 0.08; GARF, 0.40; JANE, 0.56; BUFF, 0.83; CORR, 0.78; WU, 0.79; HUMB, 0.80; KABA, 0.83; BUTL(Coh), 0.82; and BROW, 0.85. Thus, 7 of the 11 U.S. studies have only about a 20% chance of detecting a true relative risk as low as 1.5 when taken alone. Sources of bias effectively alter the power in the same direction as the bias (e.g., a downward bias in RR decreases the power). Of the potential sources of bias discussed by study in Section A.4, the predominant direction of influence on the observed RR, when identifiable, appears to be in the direction of unity, thus affecting power adversely. The RRs already have been reduced to adjust for smoker misclassification, the only systematic source of upward bias that has been established.

Studies of all sizes, large and small, are equally likely to make a false conclusion if ETS is not associated with lung cancer risk (Type I error). However, smaller studies are less likely to detect a real association when there is one (Type II error). This imbalance comes from using the significance level of the test statistic to determine whether to reject the null hypothesis. If the decision rule is to reject the hypothesis when the p-value is smaller than some prescribed value (e.g., 0.05), then the Type I error rate is 0.05, but the Type II error rate increases as study size decreases. When a study with low power fails to reject the null hypothesis of no effect, it is not very informative because that outcome may be nearly as likely when the null hypothesis is false as when it is true. When detection of a small relative risk is consequential, pooling informational content of suitably chosen studies empowers the application of statistical methods.

The heading in Table 5-9 that remains to be addressed is "relative weight," to be referred to simply as "weight." When the estimates of relative risk from selected studies are combined, as for studies within the same country as shown in the table, the logarithms of the RRs are weighted inversely proportional to their variances (see Appendix D and footnote 2 of Table 5-9). These relative weights are expressed as percentages summing to 100 for each country in Table 5-9. Study weight and power are positively associated, which is explained by the significant role of study size to both. Consequently, studies weighted most heavily (because the standard errors of the RRs are low) also tend to be the ones with the highest power (most likely to detect an effect when present).

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5.3.2. Analysis of Data by Study and Country

5.3.2.1. *Tests for Association*

The p-values of the test statistics for the hypothesis of no effect (i.e., RR = 1) are shown in Table 5-9. Values of the test statistics (the standardized log odds ratio; see Appendix D) are plotted in Figure 5-1. Also shown in Figure 5-1 for reference are the points on the horizontal axis corresponding to p-values of 0.5, 0.2, 0.1, 0.05, 0.01, and 0.001. For example, the area under the curve to the right of the vertical line labeled p = 0.01 is 0.01 (1%), so it is apparent from Figure 5-1 that three studies had significance levels $p < 0.01$ (more specifically, $0.001 < p < 0.01$). The size of the symbol (inverted triangle) used for a study is proportional in area to the relative weight of that individual study, but of current interest is the location and not the size of the symbol. If the null hypothesis is true, then the plotted values would arise from a standard normal distribution, shown in the figure (points to the left of zero indicate that the RR is less than 1, and points to the right of zero indicate that RR is greater than 1). If the points lie more toward the right side of the normal curve than would be likely to occur by chance alone, then the hypothesis of no effect is rejected in favor of a positive association between ETS exposure and lung cancer. If one constructs five intervals of equal probability (i.e., intervals of equal area under the standard normal curve), the expected number of observations in each interval is six (these five intervals are not shown on Figure 5-1). The observed numbers in these intervals, however, from left to right are 3, 3, 1, 7, and 16, an outcome that is significant at $p < 0.005$, by the chi-square goodness-of-fit test. At the points on the standard normal curve corresponding to p-values 0.5, 0.4, 0.3, 0.2, 0.1, and 0.05, the probability that a number of outcomes as large as that actually observed would occur by chance is less than 0.005 at all points. Consequently, the hypothesis of no effect is rejected on statistical grounds, and that conclusion is not attributable to a few extreme outcomes that might be aberrant in some way.

Figure 5-2 displays the U.S. studies alone (see Appendix D for calculation of the test statistics). Figure 5-3 corresponds to Figure 5-1 except that the test statistics for the hypothesis of no effect (i.e., RR = 1) for the significance levels shown apply to a single overall estimate of RR for each country, formed by statistically pooling the outcomes from the studies within each country. The areas of the symbols for countries are also in proportion to statistical weight as given in Table 5-9. It is implicitly assumed that studies within a country, and the subpopulations sampled, are sufficiently homogeneous to warrant combining their statistical results into a single estimate for the country (see Greenland [1987] for a discussion of applications of meta-analysis to epidemiology). The calculational method employed weights the observed RR from each study within a country inversely proportional to its estimated variance (see Appendix D). The relative

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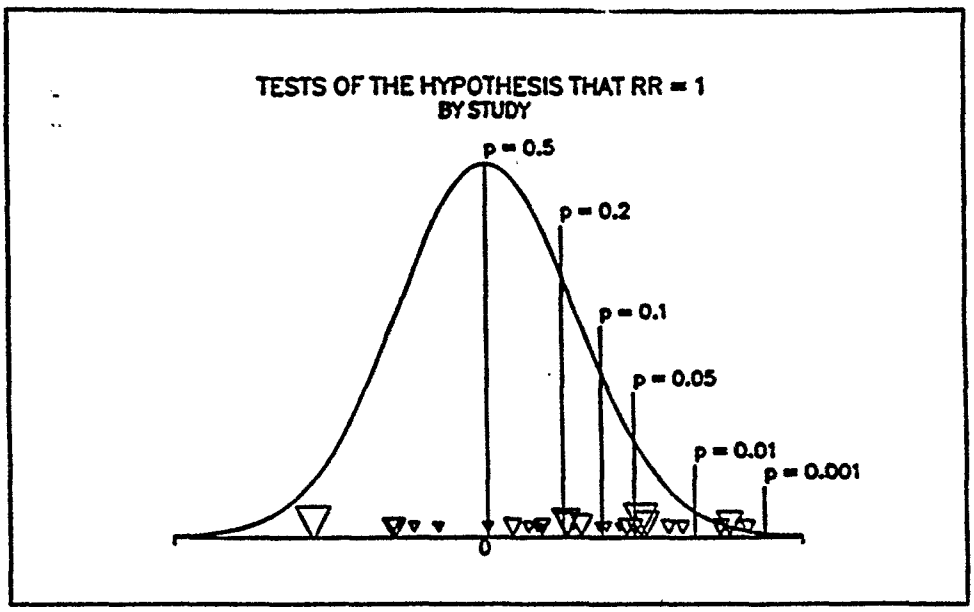

Figure 5-1. Test statistics for hypothesis RR = 1, all studies.

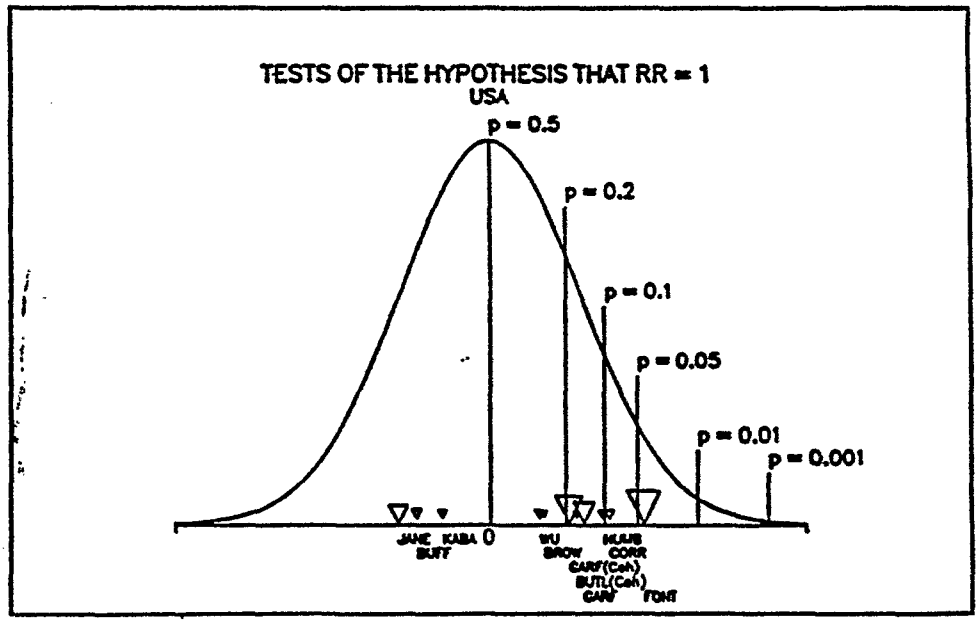

Figure 5-2. Test statistics for hypothesis RR = 1, USA only.

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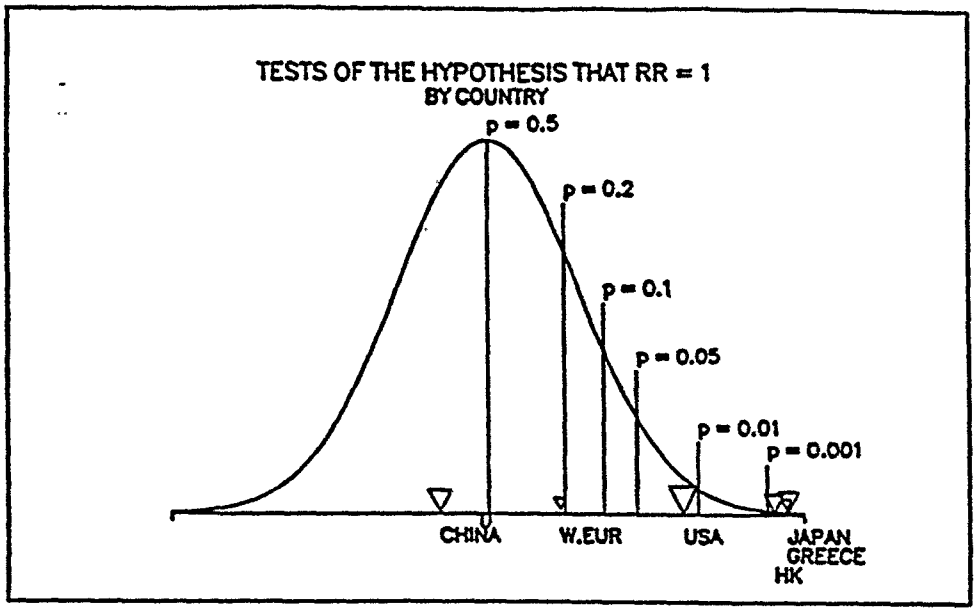

Figure 5-3. Test statistics for hypothesis RR = 1, by country.

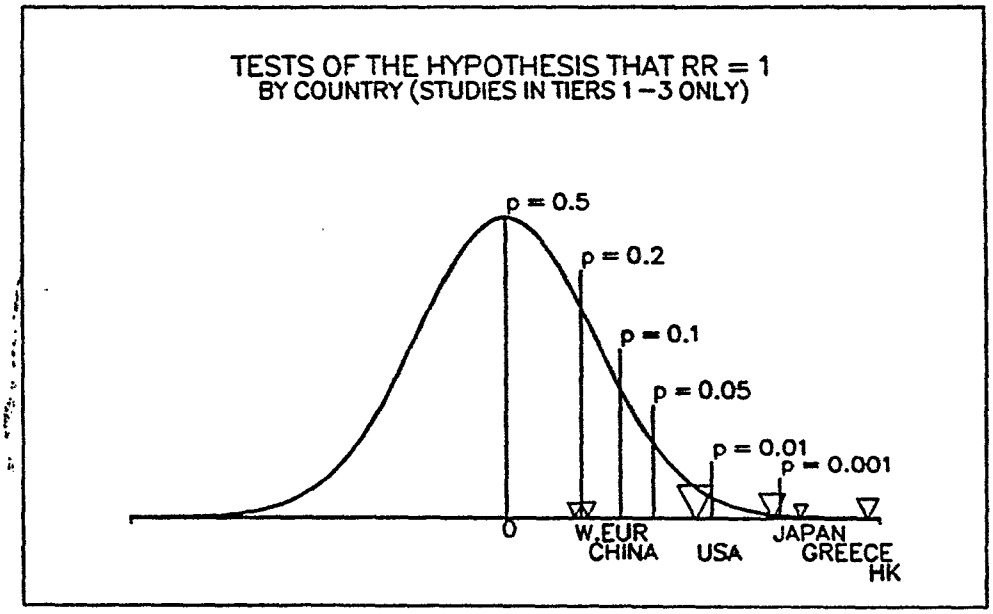

Figure 5-4. Test statistics for hypothesis RR = 1, tiers 1-3 only.

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study weights are shown in Table 5-9. Each symbol in Figures 5-1, 5-2, 5-3, and 5-4 has been scaled so that its area is proportional to the weight of the outcome represented, relative to all other outcomes shown in the same figure.

Greece, Hong Kong, and Japan, which together comprise a total weight of 39%, are *each* statistically significant at $p < 0.01$ against the null hypothesis of no increase in relative risk (RR = 1). When the United States is included, the total weight is 73%, and *each* of the four countries is significant at $p < 0.02$. The four studies combined into the group called Western Europe are not large. Together they represent 5% of the total weight, and their combined odds ratio (1.17) is slightly above 1 but not statistically significant ($p = 0.21$). In contrast, China is weighted quite high (22%), the p-value is large (0.66), and the odds ratio is less than 1 (0.95), strongly indicating no evidence of an increase in RR due to ETS. This is largely because China is very heavily influenced by WUWI (relative weight of 60% of China), which is a very large case-control study. However, this apparent inconsistency in WUWI may be due to the presence of indoor smoke from cooking and heating, which may mask any effect from passive smoking. A similar but more extreme situation is found in LIU, conducted in a locale where indoor heating with smoky coal (an established risk factor for lung cancer) and inadequate venting are common. Both WUWI and LIU were conducted primarily to assess the hazardous potential of these pollutants. The indoor environments of the populations sampled in WUWI and LIU make detection of any carcinogenic hazard from ETS unlikely, and thus render these studies to be of little value for that purpose (see discussions of WUWI and LIU in Section A.4). Without WUWI or LIU, the combined results of the two remaining studies in China, GAO and GENG, are significant at $p = 0.03$.

Such qualitative considerations about the likely utility of a study to detect an ETS effect, if one exists, are taken into account in Section 5.5. In that section, studies are ranked into one of four tiers based on their likely utility. Studies such as WUWI and LIU would be placed into Tier 4, the grouping with the least likelihood of providing useful information on the effects of ETS. Figure 5-4 is similar to Figure 5-3 displaying the distribution of test statistics for the pooled estimates by country, but includes only the studies in Tiers 1, 2, and 3; it is shown here for comparison purposes (see Section 5.5 for a detailed discussion of the analysis based on tiers).

5.3.2.2. *Confidence Intervals*

Confidence intervals for relative risk are displayed by study and by country in Table 5-9 (see Appendix D for method of calculation). The 90% confidence intervals by country are illustrated in Figure 5-5. (*Note*: 90% confidence intervals are used for correspondence to a right-

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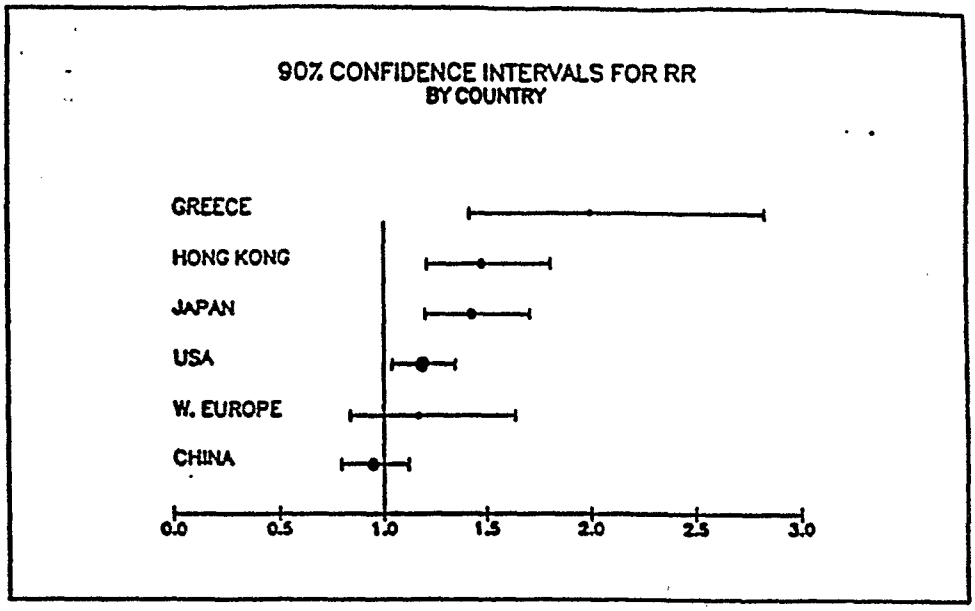

Figure 5-5. 90% confidence intervals, by country.

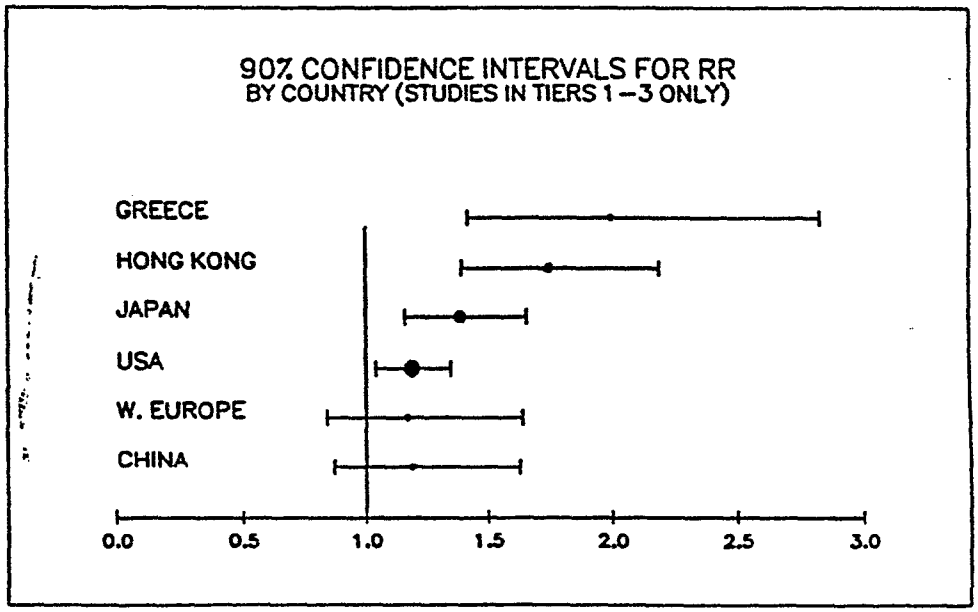

Figure 5-6. 90% confidence intervals, by country, tiers 1-3 only.

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tailed test of the hypothesis of no effect at a 5% level of significance.) The area of the symbol (solid circle) locating the point estimate of relative risk within the confidence interval is proportional to study weight. Symbol size is used as a device to draw attention to the shorter confidence intervals, which tend to be based on more data than the longer ones. The confidence intervals for countries jointly labeled as Western Europe are in Table 5-9, except for Sweden which contains two studies, PERS and SVEN. For those two studies combined, the odds ratio (OR) is 1.19 (90% C.I. = 0.81, 1.74). The confidence intervals for the pooled relative risk estimates by country for studies in Tiers 1, 2, and 3 only (see previous paragraph and Section 5.5) are displayed in Figure 5-6.

In descending order, the relative risks in Figure 5-6 are for Greece, Hong Kong, Japan, the United States, and Western Europe. (China is being excluded from this summary because it contains only one study in Tiers 1-3 [GAO], which is unlikely to be representative of such a vast country. The relative risk estimate for that study, 1.19, is similar to the overall relative risks for the United States and Western Europe.) The estimated relative risks from exposure to spousal smoking differ between countries, with Greece, Hong Kong, and Japan at the high end of the scale and the United States and Western Europe at the low end. These differences suggest that combining studies from different countries should be done with caution. The relative risks pertain only to ETS exposure from spousal smoking, which may be a higher proportion of total ETS exposure in some countries than in others. This also emphasizes the importance of taking into account exposure and background (nonspousal) ETS, which is considered in the estimation of population risk for the United States in Chapter 6.

5.3.3. Analysis of Data by Exposure Level

5.3.3.1. *Introduction*

In Section 5.3.2, analyses are conducted by individual study and by studies pooled within countries, using the dichotomous data on spousal smoking (i.e., any level of spousal smoking versus no spousal smoking) as a surrogate for ETS exposure. This section examines the response data from all of the studies that provide data analysis by exposure-level categories. Exposure level, for these studies, refers to the amount of spousal smoking. In different studies, exposure is measured by intensity (e.g., cig./day smoked by the husband), duration (e.g., number of years married to a smoker), or a combination of both (e.g., number of pack-years--packs per day $\times$ years of smoking by the husband). The data are analyzed by calculating RR estimates for the highest exposure groups only (Section 5.3.3.2) and then by testing for an upward trend in RR across exposure groups within studies as ETS exposure increases (Section 5.3.3.3).

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An evaluation of the highest exposure group or a test for exposure-related trend may be able to detect an association that would be masked in a test for effect using only dichotomous data. This masking is especially likely to occur when dealing with a weak association or a crude surrogate measure for exposure that is widespread (i.e., greater potential for exposure misclassification), both of which are difficulties in studies of ETS and lung cancer.

As discussed in Chapter 3, ETS is a dilute mixture, and, consequently, any association observed between environmental levels of ETS exposure and lung cancer is likely to be weak (i.e., have a low RR). Furthermore, questionnaire-based assessment of exposure to ETS is a crude indicator of actual lifetime exposure, and spousal smoking is an incomplete surrogate for exposure because it does not consider ETS from other sources, such as the workplace. Therefore, exposure misclassification in both directions is inevitable. For example, there will be women whose husbands do not smoke but who are exposed to substantial levels of ETS from other sources, and there will be women whose husbands smoke but who are not actually exposed to appreciable levels of ETS. This latter scenario is most likely if the level of spousal smoking is low. Comparing the highest exposure group with the "unexposed" group will help reduce the effect of this latter type of exposure misclassification bias.

In addition, the detection of an exposure-response relationship (trend) across exposure groups increases support for a causal association by diminishing the likelihood that the results can be explained by confounding, because any potential confounder would have to be associated with both lung cancer and ETS exposure in a dose-related manner. However, the potential for exposure misclassification is compounded when the exposed group is further divided into level-of-exposure categories and the sample sizes become small. This is especially problematic in small studies. These inherent difficulties with the ETS database tend to diminish the possibility of detecting exposure-response relationships. Therefore, the inability to demonstrate an exposure-response trend is not considered evidence against causality; rather, if a statistically significant trend can be detected despite these potential obstacles, it provides evidential support for a causal association.

5.3.3.2. *Analysis of High-Exposure Data*

In this section, analyses will be conducted for the highest exposure groups by study and by studies pooled within countries. As described in Section 5.3.3.1, analyzing only the data from the highest exposure group of each study increases the sensitivity for detecting an association and reduces the effects of exposure misclassification. Fractionating the data, however, does decrease the power to observe statistical significance.

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The results of statistical inference using only data from the highest exposure categories are displayed in Table 5-10. As indicated in the table, exposure-level data are available in 17 studies. The definitions of highest exposure category, shown next to the study name in the table, vary widely between studies. Crude RR estimates adjusted for smoker misclassification (see Section 5.2 and Appendix B) are used in this section rather than the estimates adjusted for modifying factors within the studies, because the latter are available by exposure level for only a limited number of studies.

Several observations are apparent from Table 5-10. First, every one of the 17 individual studies shows increased risk at the highest exposure level, even after adjusting for smoker misclassification. Second, 9 of the 16 comparisons for which sufficient data are available are statistically significant ($p \leq 0.05$), despite most having very low statistical power. Third, the RR estimates pooled within countries are each statistically significant with $p \leq 0.02$. Although the RR estimates within a country are pooled across different definitions of highest exposure, which somewhat limits their interpretation and practical value, it is apparent that these RRs are considerably higher than the values observed for the dichotomous data (Table 5-9). The RR estimates pooled by country vary from a low of 1.38 ($p = 0.005$) for the United States to a high of 3.11 ($p = 0.02$) for Western Europe, which contains only one study. Finally, the overall pooled estimate of 1.81 for the highest exposure groups from all 17 studies is highly statistically significant ($p < 0.000001$).

These results are consistent with the statistical evidence presented in Section 5.3.2 for an association between ETS exposure and lung cancer. In fact, increased risks are found for the highest exposure groups without exception. Furthermore, the RR estimates pooled within countries are all statistically significant and range from 1.38 to 3.11, even after adjustment for smoker misclassification. The consistency of these highest exposure results cannot be accounted for by chance, and the stronger associations detected for the highest exposure groups across all countries further reduce the likelihood that bias or confounding could explain the observed relationship between ETS and lung cancer.

In addition, with the exception of Western Europe, which contains only one low-power study in this analysis, the pooled RR estimates from other, more "traditional" countries are all appreciably higher than that from the United States. It is likely that these differences are at least partially a result of higher background (nonspousal) ETS exposures to the allegedly "unexposed" group in the United States. Again, this highlights the importance of accounting for ETS exposures from sources other than spousal smoking. An adjustment for background ETS exposures is made in Chapter 6, for the estimation of population risk for the United States.

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Table 5-10. Statistical measures for highest exposure categories only[1]

Location	Study	Highest exposure level	Relative weight[2] (%)	P-value Power[3]	P-value Effect[4]	RR[5,6]	Confidence interval[6] 90%
Greece	KALA	(≥41 cig./day)	35	0.06	0.16	1.57	(0.74, 3.32)
Greece	TRIC	(≥21 cig./day)	65	0.11	0.003	2.55	(1.46, 4.42)
Greece	All	High	8		0.002	2.15	(1.38, 3.35)
Hong Kong	KOO	(≥21 cig./day)	36	0.11	0.36	1.18	(0.58, 2.55)
Hong Kong	LAMT	(≥21 cig./day)	64	0.16	0.02	2.05	(1.18, 3.57)
Hong Kong	All	High	8		0.03	1.68	(1.06, 2.62)
Japan	AKIB	(≥30 cig./day)	6	0.10	0.13	2.1	(0.7, 2.5)
Japan	HIRA (Coh)	(≥20 cig./day)	89	0.13	0.00015	1.91	(1.42, 2.56)
Japan	INOU	(≥20 cig./day)	4	•	0.05	3.09	(1.0, 11.8)
Japan	All	High	22		<0.00004	1.96	(1.49, 2.60)
United States	CORR	(≥41 pack-yrs)	8	0.06	0.005	3.20	(1.53, 6.74)
United States	FONT	(≥80 pack-yrs)	14	•	0.21	1.32[7]	(0.75, 2.29)
United States	GARF	(≥20 cig./day)	15	0.21	0.01	2.05	(1.19, 3.49)
United States	GARF (Coh)	(≥20 cig./day)	45	•	0.33	1.09	(0.81, 1.49)
United States	HUMB	(≥21 cig./day)	2	•	0.46	1.09	(0.27, 4.73)
United States	JANE	(≥50 pack-yrs)	8	•	0.50	1.01	(0.50, 2.04)
United States	WU	(≥31 years)	8[8]	•	•	1.87	•
United States	All	High	36		0.005	1.38	(1.13, 1.70)
W. Europe	PERS	(≥16 cig./day)	100	•	0.02	3.11	(1.18, 7.71)
W. Europe	All	High	2		0.02	3.11	(1.18, 7.71)
China	GAO	(≥40 years)	35	0.33	0.02	1.7	(1.09, 2.65)
China	GENG	(≥20 cig./day)	65	•	<0.00001	2.76	(2.02, 3.84)
China	All	High	24		<0.000001	2.32	(1.78, 3.03)
All	All	High			<0.000001	1.81	(1.60, 2.05)

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Table 5-10. (continued)

[1]Similar to Table 5-9 except entries apply to highest exposure category only in each study. Only studies with data available for categorized measures of exposure are included. Relative risks and confidence bounds are corrected for smoker misclassification.
[2]A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3]*A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4]One-sided p-value for test of RR = 1 versus RR > 1.
[5]Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[6]Values may differ from those of Table 5-11, where confidence intervals are shown as they appear in the source. In Table 5-11, the RR and confidence interval are *not* corrected for smoker misclassification, as in this table, and most of the confidence intervals are 95% instead of 90%.
[7]Value shown is for all cell types with the two control groups combined. For adenocarcinoma cases only, the RR is 1.68 with C.I. = 0.81, 3.46.
[8]Relative weight assumed to be the same as for CORR, based on the outcome in Table 5-9.

*Data not available.

5.3.3.3. *Tests for Trend*

In this section, exposure-response data from the studies providing data by exposure level are tested for upward trend. An exposure-response relationship provides strong support for a causal association (see Section 5.3.3.1).

Table 5-11 presents the female exposure-response data and trend test results from the studies of ETS and lung cancer discussed in this report. The p-values reported in the table are for a test of no trend against the one-sided alternative of an upward trend (i.e., increasing RR with increasing exposure). (*Note*: The results for tests of trend are taken from the study reports. Unless the report specified that a one-sided alternative was used, the reported p-value was halved to reflect the outcome for the one-sided alternative of RR increasing with exposure. Where the data are available, the p-values reported by the individual study's authors have been verified here by application of the Mantel, Haenszel test [Mantel, 1963].)

Wu-Williams and Samet (1990) previously reviewed the exposure-response relationships from the epidemiologic studies on ETS then available. They determined that 12 of 15 studies were statistically significant for the trend test for at least one exposure measure. The probability of this proportion of statistically significant results occurring by chance in this number of studies is virtually zero ($p < 10^{-13}$). Intensity of spousal smoking was the most consistent index of ETS exposure for the demonstration of an exposure-response relationship.

Our assessment of the exposure-response data is similar and provides essentially the same results for a slightly different set of studies. Table 5-12 summarizes the p-values of the trend

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Table 5-11. Exposure response trends for females

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
AKIB	21	82		1.0		0.03
(cig./day)	29	90	1-19	1.3	(0.7, 2.3)[5]	
	22	54	20-29	1.5	(0.8, 2.8)[5]	
	12	23	≥30	2.1	(0.7, 2.5)[5]	
AKIB	21	82	0	1.0		0.24
(years)	20	30	1-9	2.1	(1.0, 4.3)[5]	
	29	81	20-39	1.5	(0.8, 2.7)[5]	
	22	59	≥40	1.3	(0.7, 2.5)[5]	
CORR	8	72	0	1.00		0.01
(pack-yrs.)	5	38	1-40	1.18	(0.44, 3.20)	
	9	23	≥41	3.52	(1.45, 8.59)	
FONT[6]	*	*	0	1.00		0.07
(years)	*	*	1-15	1.19	(0.88, 1.61)	
	*	*	16-30	1.14	(0.82, 1.59)	
	*	*	>30	1.25	(0.91, 1.72)	
FONT[7]	*	*	0	1.00		0.02
(years)	*	*	1-15	1.33	(0.93, 1.89)	
	*	*	16-30	1.40	(0.96, 2.05)	
	*	*	>30	1.43	(0.99, 2.09)	
FONT[6]	*	*		1.00		0.04
(pack-yrs.)	*	*	0<15	0.96	(0.72, 1.29)	
	*	*	15-39	1.13	(0.81, 1.59)	
	*	*	40-79	1.25	(0.86, 1.81)	
	*	*	≥80	1.33	(0.68, 2.58)	
FONT[7]	*	*		1.00		0.01
(pack-yrs.)	*	*	0<15	1.03	(0.73, 1.46)	
	*	*	15-39	1.26	(0.85, 1.87)	
	*	*	40-79	1.49	(0.98, 2.27)	
	*	*	≥80	1.70	(0.82, 3.49)	
GAO	99	57	0-19	1.0		0.29
(tot. yrs.)[8]	93	63	20-29	1.1	(0.7, 1.8)	
	107	78	30-39	1.3	(0.8, 2.1)	
	76	48	≥40	1.7	(1.0, 2.9)	
GARF	44	157	0	1.00		<0.02
(cig./day)	29	90	1-9	1.15	(0.8, 1.6)	
	17	56	10-19	1.08	(0.8, 1.5)	
	26	44	≥20	2.11	(1.1, 4.0)	
GENG	*	*	0	1.00		<0.05[9]
(cig./day)	*	*	1-9	1.40	(1.1, 1.8)	
	*	*	10-19	1.97	(1.4, 2.7)	
	*	*	≥20	2.76	(1.9, 4.1)	

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Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
GENG	*	*	0	1.00		<0.05[9]
(years)	*	*	<20	1.49	(1.15, 1.94)	
	*	*	20-39	2.23	(1.54, 3.22)	
	*	*	≥40	3.32	(2.11, 5.22)	
HUMB	*	*	0	1.0		ns
(cig./day)	*	*	1-20	1.8	(0.6, 5.6)[5]	
	*	*	≥21	1.2	(0.3, 5.2)[5]	
INOU	*	*	0-4	1.00		<0.03
(cig./day)	*	*	5-19	1.58	(0.4, 5.7)[5]	
	*	*	≥20	3.09	(1.0, 11.8)[5]	
JANE[10]	*	*	0	1.00		*
(pack-yrs.)	*	*	1-24	0.71	(0.37, 1.35)	
	*	*	25-49	0.98	(0.47, 2.05)	
	*	*	≥50	1.10	(0.47, 2.56)	
KALA	26	46	0	1.00		0.08
(cig./day)	34	39	1-20	1.54	(0.88, 2.70)	
	22	22	21-40	1.77	(0.93, 3.35)	
	8	9	41+	1.57	(0.64, 3.85)	
KALA	26	46	0	1.00		0.04
(years)	15	21	<20	1.26	(0.56, 2.87)	
	15	20	20-29	1.33	(0.58, 3.03)	
	17	15	30-39	2.01	(0.86, 4.67)	
	17	16	≥40	1.88	(0.82, 4.33)	
KOO	32	67	0	1.00		0.16
(cig./day)	17	15	1-10	2.33	(0.9, 5.9)	
	25	35	11-20	1.74	(0.8, 3.8)	
	12	19	≥21	1.19	(0.5, 3.0)	
LAMT[6]	84	183	0	1.00		0.01
(cig./day)	22	22	1-10	2.18	(1.14, 4.15)	
	56	66	11-20	1.85	(1.19, 2.87)	
	20	21	≥21	2.07	(1.07, 4.03)	
LAMT[7]	53	92	0	1.00		0.01
(cig./day)	17	12	1-10	2.46	(1.09, 5.54)	
	37	28	11-20	2.29	(1.26, 4.16)	
	15	9	≥21	2.89	(1.18, 7.07)	

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Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
PERS[11]	34	*	0	1.0		0.12
(cig./day)	26	*	1-15	1.0	(0.6, 1.8)	
	7	*	≥16	3.2	(1.0, 9.5)	
TRIC[12]	24	109	0	1.00		0.01
(cig./day)	24	56	1-20	1.95	(1.13, 3.36)	
	14	25	≥21	2.55	(1.31, 4.93)	
WU[13]	*	*	0	1.0		*
(years	*	*	1-30	1.2	*	
exposed as	*	*	≥31	2.0	*	
adult)						
GARF(Coh)[14]	65	*	0	1.00		*
	39	*	1-19	1.27	(0.85, 1.89)	
(cig./day)	49	*	≥20	1.10	(0.77, 1.61)	
HIRA(Coh)[15]	37	21,895	0	1.00		0.01
	99	44,184	1-19[16]	1.41	(1.03, 1.94)	
(cig./day)	64	25,461	≥20	1.93	(1.35, 2.74)	

[1]Smoking by spouse unless otherwise specified.
[2]See footnote 6 in Table 5-10.
[3]Confidence intervals are 95% unless noted otherwise.
[4]P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative (i.e., upward trend). Values below 0.01 are shown as 0.01.
[5]90% confidence interval.
[6]All histologies.
[7]Adenocarcinomas only.
[8]Years lived with a smoking husband.
[9]Neither crude data nor a test for trend is included in reference articles. The relative risk at each exposure category is significant alone, however, at $p < 0.05$.
[10]Data are from subject responses in Table 3 of the source.
[11]Low exposure level is for husband smoking up to 15 cigarettes per day or one pack (50 g) of pipe tobacco per week, or smoking any amount during less than 30 years of marriage. High exposure level is for husband smoking more than 15 cigarettes per day or one pack of pipe tobacco per week during 30 years of marriage or more.
[12]Data from Trichopoulos et al. (1983), with RRs corrected (personal communication from Trichopoulos, 1984).
[13]Years of exposure to spousal smoke *plus* years of exposure to workplace smoke; adenocarcinomas only.
[14]Value under "RR" is mortality ratio of observed to expected lung cancer deaths. Value under "Case" is number of observed lung cancer deaths.
[15]Standardized for age of subject (Hirayama, 1984). Values under "case" are numbers of lung cancer deaths; values under "cont." are total population.
[16]Includes former smokers of any exposure level.

*Data not available; ns = not significant.

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Table 5-12. Reported p-values of trend tests for ETS exposure by study[1]

	Trend test results		
	Intensity (cig./day)	Duration (total years)	Cumulative (pack-years)[2]
AKIB	0.03	0.24	*
CORR	*	*	0.01
FONT	*	0.07[3]	0.04
	*	<0.02[4]	<0.01
GAO	*	0.29	*
GARF	<0.02	*	*
GENG	<0.05[5]	<0.05[5]	*
HUMB	ns	*	*
INOU	<0.03	*	*
JANE	*[6]	*	*
KALA	0.08	0.04	*
KOO	0.16	*	*
LAMT	<0.01	*	*
	<0.01[4]		
PERS	0.12	*	*
TRIC	<0.01	*	*
WU	*	*[6]	*
GARF(Coh)	*[6]	*	*
HIRA(Coh)	<0.01	*	*

[1]Detailed data presented in Table 5-11.
[2]A "pack-year" is equivalent to one pack/day for 1 year.
[3]All cell types.
[4]Adenocarcinoma only.
[5]See footnote 9 in Table 5-11.
[6]Trend results presented without p-values or raw data--see Table 5-11.

*Data not available; ns = not significant.

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tests for the various ETS exposure measures from the studies presented in Table 5-11. The exposure measure most commonly used was intensity of spousal smoking. Eight of the twelve studies that reported exposure-response data based on cigarettes per day showed statistical significance at the $p < 0.05$ level for the trend test. Again, the probability of this many statistically significant results occurring by chance in this number of studies is negligible ($p < 10^{-7}$). The trend test results for the other exposure measures were consistent, in general, with those based on cigarettes per day (three of six studies using total years of exposure were significant, as were two of two studies using pack-years).

Overall, 10 of the 14 studies with sufficient exposure-response data show statistically significant trends for one or more exposure measures. No possible confounder has been hypothesized that could explain the increasing incidence of lung cancer with increasing exposure to ETS in so many independent studies from different countries.

By country, the number of studies with significant results for upward trend is as follows: China, 1 of 2; Greece, 2 of 2; Hong Kong, 1 of 2; Japan, 3 of 3; Sweden, 0 of 1; and United States, 3 of 4. Of particular interest, two of the U.S. studies, GARF and CORR, are statistically significant for a test of trend, providing evidence for an association between ETS exposure and lung cancer even though neither was significant in a test for effect. In both cases, this occurs because the data supporting an increase in RR are largely at the highest exposure level. It appears that relatively high exposure levels are necessary to observe an effect in the United States, as would be expected if spousal smoking is a weaker surrogate for total ETS exposure in this country.

The U.S. study by Fontham et al. (1991), a well-conducted study and the largest case-control study of ETS and lung cancer to date, with the greatest power of all the U.S. studies to detect an effect, was statistically significant with a p-value of 0.04 for the trend test with pack-years as the exposure measure. When the analysis was restricted to adenocarcinomas (the majority of the cases), tests for trend were statistically significant by both years ($p = 0.02$) and pack-years ($p = 0.01$).

5.3.4. Conclusions

Two types of tests have been conducted: (1) a test for effect, wherein subjects must be classified as exposed or unexposed to ETS, generally according to whether the husband is a smoker or not, and (2) a trend test, for which exposed subjects are further categorized by some level of exposure, such as the number of cigarettes smoked per day by the husband, duration of smoking, or total number of packs smoked. Results are summarized in Table 5-13, with countries in the same order as in Table 5-9. Studies are noted in boldface if the test of effect or the trend

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Table 5-13. P-values of tests for effect and for trend by individual study[1]

Country	Study	Power	Test	P-value[2]
Greece	KALA	0.39	Effect	0.02
			Trend	0.04
Greece	TRIC	0.45	Effect	<0.01
			Trend	<0.01
Hong Kong	CHAN	0.43	Effect	>0.50
Hong Kong	KOO	0.43	Effect	0.06
			Trend	0.16
Hong Kong	LAMT	0.73	Effect	<0.01
			Trend	<0.01
Hong Kong	LAMW	0.39	Effect	<0.01
Japan	AKIB	0.42	Effect	0.05
			Trend	0.03
Japan	HIRA(Coh)	0.75	Effect	0.04
			Trend	<0.01
Japan	INOU	0.17	Effect	0.07(0.05)[3]
			Trend	0.03
Japan	SHIM	0.37	Effect	0.38
Japan	SOBU	0.66	Effect	0.01
United States	BROW	0.15	Effect	0.28
United States	BUFF	0.17	Effect	>0.50
United States	BUTL(Coh)	0.18	Effect	0.17
United States	CORR	0.22	Effect	0.10(0.005)[3]
			Trend	0.01
United States	FONT	0.93	Effect	0.03[4]
			Trend	0.04[4]
United States	GARF	0.60	Effect	0.12(0.01)[3]
			Trend	<0.02
United States	GARF(Coh)	0.92	Effect	0.18

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Table 5-13. (continued)

Country	Study	Power	Test	P-value[2]
United States	HUMB	0.20	Effect Trend	0.10 ns
United States	JANE	0.44	Effect	>0.50
United States	KABA	0.17	Effect	>0.50
United States	WU	0.21	Effect	0.29
W. Europe				
Scotland	Hole(Coh)	0.09	Effect	0.26
England	LEE	0.20	Effect	0.50
Sweden	PERS	0.45	Effect Trend	0.27(0.02)[3] 0.12
Sweden	SVEN	0.24	Effect	0.31
China	GAO	0.66	Effect Trend	0.18(0.02)[3] 0.29
China	GENG	0.32	Effect Trend	0.01 <0.05
China	LIU	0.18	Effect	>0.50
China	WUWI	0.89	Effect	>0.50

[1]Test for effect--H_0: no increase in lung cancer incidence in never-smokers exposed to spousal ETS; H_A: an increase. Test for trend--H_0: no increase in lung cancer incidence as exposure to spousal ETS increases; H_A: an increase. P-values less than 0.05 are in boldface.
[2]Smallest p-value is used when there is more than one test for trend; ns = not significant.
[3]P-value in parentheses applies to test for effect at highest exposure only (see text).
[4]For all cell types. P-values for adenocarcinoma alone were smaller.

test is significant at 0.05 (one-tailed) or if, as in PERS and GAO, only the odds ratio at the highest exposure is significant. In 8 of the 11 studies in Greece, Hong Kong, or Japan, at least one of the tests is significant at 0.05. For the United States and Western Europe, 4 of the 15 studies are significant at 0.05 for at least one test. For the studies within the first group of countries (Greece, Hong Kong, and Japan), the median power is 0.43, and only 1 of the 10 studies (10%) has power less than 0.25 (INOU). In contrast, the median power for the United States and Western Europe together is 0.21, and 10 of the 15 studies (67%) have power less than 0.25. In a

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small study, significance is meaningful, but nonsignificance is not very informative because there is little chance of detecting an effect when there is one. Consequently, there are several studies in the United States-Western Europe group that provide very little information. Two of the four studies in China are significant at the 0.05 level for at least one test. The two nonsignificant studies in China (LIU and WUWI) are not very informative on ETS for reasons previously described (see Section 5.3.2.1).

For the U.S. and Western Europe studies, 3 of the 5 with power greater than 0.25 are shown in boldface (FONT, GARF, and PERS), indicating at least suggestive evidence of an association between ETS and lung cancer, compared with only 1 of 10 with power under 0.25 (CORR). All three of the higher power studies are significant for effect (PERS and GARF are significant at the highest exposure only) and two (FONT and GARF) are also significant for trend. CORR is significant for trend and for effect at the highest exposure level. Overall, the evidence of an association in the United States and Western Europe is strengthened by the tests at the highest exposure levels and by the tests for trend.

To summarize, the results of the several different analyses in this section provide substantial evidence that exposure to ETS from spousal smoking is associated with increased lung cancer mortality. The evidence is strongest in Greece, Hong Kong, Japan, and the United States. The evidence for Western Europe appears similar to that in the United States, but there are far fewer studies. (The usefulness of statistical information from studies in China is quite limited, so no conclusions are drawn from the studies there.)

The evidence from the individual studies, without pooling within each country, is also conclusive of an association. Adjustment, on an individual study basis, for potential bias due to smoker misclassification results in slightly lower relative risk estimates but does not affect the overall conclusions. The results based on either the test for effect or the test for trend cannot be attributed to chance alone. Tests for effect, tests at the highest exposure levels, and tests for trend jointly support the conclusion of an association between ETS and lung cancer in never-smokers.

5.4. STUDY RESULTS ON FACTORS THAT MAY AFFECT LUNG CANCER RISK

5.4.1. Introduction

The possibility of chance accounting for the observed associations between ETS and lung cancer has been virtually ruled out by the statistical methods previously applied. Potential sources of bias and confounding must still be considered to determine whether they can explain the observed increases. While the exposure-response relationships reviewed in Section 5.3.3.3 generally reduce the likelihood of bias and confounding accounting for the observed associations, this section focuses on specific factors that may bias or modify the lung cancer results.

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Validity is the most relevant concern for hazard identification. Generalizability of results to the national population (depending on "representativeness" of the sample population, treated in the text) is important for the characterization of population risk, but no more so than validity. As stated by Breslow and Day (1980), "In an analysis, the basic questions to consider are the degree of association between risk for disease and the factors under study, the extent to which the observed associations may result from bias, confounding and/or chance, and the extent to which they may be described as causal."

Whereas Section 5.3 examined the epidemiologic data by individual study and by pooling results by country, this section considers potential sources of bias and confounding and their implications for interpretation of study results. As indicated in the brief review of the meanings of bias and confounding at the end of this section, confounding arises from the characteristics of the sample population, whereas bias is the result of individual study features involving design, data collection, or data analysis. Section 5.4.2 briefly reviews the evidence on non-ETS risk factors and modifiers of lung cancer incidence that appears in the 30 epidemiologic studies (not counting KATA) reviewed for this report. None of the factors has been established as a confounder of ETS, which would require demonstrating that the factor causes lung cancer and is correlated with ETS exposure (specifically, spousal smoking to affect the analysis in this report).

Our objective is to consider the influence of sources of uncertainty on the statistical measures summarized in Table 5-13, although there are limitations to such an endeavor. For example, not controlling for a factor such as age in the statistical analysis, which should be done whether or not the study design is matched on age, may require reanalyzing data not included in the study report. Potential sources of bias are just that--*potential*--and their actual effect may be impossible to evaluate (e.g., selection bias in case-control studies). Although numerous questions of interest cannot be answered unequivocally, or even without a measure of subjective judgment, it is nevertheless worthwhile to consider issues that may affect interpretation of the quantitative results. The issues of concern are largely those of epidemiologic investigations in general that motivate the conscientious investigator to implement sound methodology. Statistical uncertainty aside, the outcomes of studies that fare well under close examination inspire more confidence and thus deserve greater emphasis than those that do poorly.

Preliminary to the next sections, some relevant notes on epidemiologic concepts are excerpted from two IARC volumes entitled *Statistical Methods in Cancer Research* (Breslow and Day, 1980, 1987), dealing with case-control and cohort studies, respectively, which are excellent references. In the interest of brevity, an assortment of relevant passages is simply quoted directly from several locations in the references (page numbers and quotation marks have been omitted to

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improve readability). Some readers may wish to skip to the next section; those interested in a more fluid, cogent, and thorough presentation are referred to the references.

- Bias and confounding. The concepts of bias and confounding are most easily understood in the context of cohort studies, and how case-control studies relate to them.. Confounding is intimately connected to the concept of causality. In a cohort study, if some exposure E is associated with disease status, then the incidence of the disease varies among the strata defined by different levels of E. If these differences in incidence are caused (partially) by some other factor C, then we say that C has (partially) confounded the association between E and the disease. If C is not causally related to disease, then the differences in incidence cannot be caused by C, thus C does not confound the disease/exposure association.

  Confounding in a case-control study has the same basis as in a cohort study . . . and cannot normally be removed by appropriate study design alone. An essential part of the analysis is an examination of possible confounding effects and how they may be controlled.

  Bias in a case-control study, by contrast, [generally] arises from the differences in design between case-control and cohort studies. In a cohort study, information is obtained on exposures before disease status is determined, and all cases of disease arising in a given time period should be ascertained. Information on exposure from cases and controls is therefore comparable, and unbiased estimates of the incidence rates in the different subpopulations can be constructed. In case-control studies, however, information on exposure is normally obtained after disease status is established, and the cases and controls represent samples from the total. Biased estimates of incidence ratios will result if the selection processes leading to inclusion of cases and controls in the study are different (selection bias) or if exposure information is not obtained in a comparable manner from the two groups, for example, because of differences in response to a questionnaire (recall bias). Bias is thus a consequence of the study design, and the design should be directed towards eliminating it. The effects of bias are often difficult to control in the analysis, although they will sometimes resemble confounding effects and can be treated accordingly.

  To summarize, confounding reflects the causal association between variables in the population under study, and will manifest itself similarly in both cohort and case-control studies. Bias, by contrast, is not a property of the underlying population. It results from inadequacies in the design of case-control studies, either in the selection of cases or controls or from the manner in which the data are acquired.

- On prospective cohort studies. One of the advantages of cohort studies over case-control studies is that information on exposure is obtained before disease status is ascertained. One can therefore have considerable confidence that errors in measurement are the same for individuals who become cases of the disease of interest, and the remainder of the cohort. The complexities possible in retrospective case-control studies because of differences in recall between cases and controls do not apply. [Regarding the success of a cohort study, the] follow-up over time . . . is the essential feature. . . . The success with which the follow-up is achieved is probably the basic measure of the quality of the study. If a substantial proportion of the cohort

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is lost to follow-up, the validity of the study's conclusions is seriously called into question.

- On case-control studies. Despite its practicality, the case-control study is not simplistic and it cannot be done well without considerable planning. Indeed, a case-control study is perhaps the most challenging to design and conduct in such a way that bias is avoided. Our limited understanding of this difficult study design and its many subtleties should serve as a warning--these studies must be designed and analyzed carefully with a thorough appreciation of their difficulties. This warning should also be heeded by the many critics of the case-control design. General criticisms of the design itself too often reflect a lack of appreciation of the same complexities which make these studies difficult to perform properly.

  The two major areas where a case-control study presents difficulties are in the selection of a control group, and in dealing with confounding and interaction as part of the analysis. . . these studies are highly susceptible to bias, especially selection bias which creates non-comparability between cases and controls. The problem of selection bias is the most serious potential problem in case-control studies. . . . Other kinds of bias, especially that resulting from non-comparable information from cases and controls are also potentially serious; the most common of these is recall . . . bias which may result because cases tend to consider more carefully than do controls the questions they are asked or because the cases have been considering what might have caused their cancer.

In addition to standard demographic factors (e.g., age) that are usually controlled for in a study, a number of other variables have been considered as potential risk factors (including risk modifiers) for lung cancer. If a factor increases the risk of lung cancer and its presence is correlated with exposure to spousal ETS, then it could be a confounder of ETS if not controlled for in a study's analysis. In general, factors that may affect risk of lung cancer and also may be correlated with ETS exposure are of interest as possible explanatory variables. Findings from the ETS studies are reviewed for six general categories: (1) personal history of lung disease, (2) family history of lung disease, (3) heat sources, (4) cooking with oil, (5) occupation, and (6) diet. Table 5-14 provides an overview of results in these categories. Two shortcomings are common in the studies where these factors appear: failure to evaluate the correlation of exposure to the factor and to ETS, and then to adjust the analysis accordingly; and failure to adjust significance levels for multiple comparisons. Multiple tests on the same data increase the chance of a false positive (i.e., outcomes appear to be more significant than warranted due to the multiple comparisons being made on the same data).

5.4.2. History of Lung Disease

Results regarding history of lung disease have been reported in eight of the reviewed ETS studies, but with little consistency. Tuberculosis (TB), for example, is significantly associated with lung cancer in GAO (OR = 1.7; 95% C.I. = 1.1, 2.4) but not in SHIM (OR = 1.1, no other

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Table 5-14. Other risk-related factors for lung cancer evaluated in selected studies

Category	Possible risk factor	Mixed outcome	No evidence
Personal or family history	WU (US) GENG (Ch) LIU (Ch)	SHIM (Jap) GAO (Ch)	
Heat source for cooking or heating	WU (US) WUWI (Ch) GENG (Ch) GAO (Ch) LIU (Ch)	SOBU (Jap)	LAMW (HK)
Cooking with oil	WUWI (Ch) GAO (Ch)		
Diet	WU (US)	KALA (Gr) HIRA (Jap)	SHIM (Jap)
β-carotene			WUWI (Ch) KALA (Gr) GAO (Ch)-harmful
Occupation	WUWI (Ch) SHIM (Jap) GENG (Ch) BUTL (US) BUFF (US)		WU (US) GAO (Ch)

statistics), LIU or WU (no ORs provided). Chronic bronchitis, on the other hand, is nonsignificant in GAO (OR = 1.2; 95% C.I. = 0.8, 1.7), SHIM (OR = 0.8), KABA, and WU, but it is highly significant in LIU (OR = 7.37; 95% C.I. = 2.40, 22.66 for females; OR = 7.32; 95% C.I. = 2.66, 20.18 for males) and mildly so in WUWI (OR = 1.4; 95% C.I. = 1.2, 1.8). (Notably, the populations of WUWI, LIU, and GENG were exposed to non-ETS sources of household smoke.) Consideration of each lung disease separately, as presented, ignores the effect of multiple comparisons described above. For example, GAO looked at five categories of lung disease. If that were taken into account, TB would no longer be significant. No discussion of the multiple comparisons effect was found in any of the references, which might at least be acknowledged.

Broadening our focus to examine the relationship of lung cancer to history of lung disease in general does little to improve consistency. GENG reports an adjusted OR of 2.12 (95% C.I. = 1.23, 3.63) for history of lung disease, GAO's disease-specific findings are consistently positive, and WUWI reports three positive associations out of an unknown number assessed. SHIM and

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WU, however, consistently found no effect except marginally for silicosis (perhaps better construed as an occupational exposure surrogate) in SHIM and for childhood pneumonia in WU. LIU found a significant association only for chronic bronchitis and KABA only for pneumonia. Interpretation is hampered by the lack of numerical data for factors that were not statistically significant in KABA, LIU, and WU. Even with such data, however, interpretation is hampered by the absence of control for key potential confounders in many of the studies (e.g., age in GENG and LIU). Only one study (WU) attempted to control for a history variable (childhood pneumonia), which reportedly did not alter the ETS results. The importance of prior lung disease as a factor in studies of ETS is thus unclear, but it does not appear to distort results one way or the other.

5.4.3. Family History of Lung Disease

Only a few of the studies addressed family history of lung disease. GAO found no significant association between family history of lung cancer and subjects' disease status (e.g., parental lung cancer OR = 1.1; 95% C.I. = 0.6, 2.3), and positive family histories were very rare (e.g., 1.0% among mothers of either cases or controls). In contrast, WUWI reports a significant association with history of lung cancer in first-degree relatives (OR = 1.8; 95% C.I. = 1.1, 3.0), which occurred in about 4.5% of the cases. The presence of TB in a household member (OR = 1.6; 95% C.I. = 1.2, 2.1) is also significant, even after adjustment for personal smoking and TB status. The rarity of family-linked lung cancer in these populations makes accurate assessment difficult and also reduces the potential impact on results of any effect it may have. Its study in populations where such cancer is more common would be more appropriate. The household TB outcome may be the result of multiple comparisons and/or confounding, particularly in view of the weaker (nonsignificant) outcome noted for *personal* TB status.

5.4.4. Heat Sources for Cooking or Heating

Household heating and cooking technologies have received considerable attention as potential lung cancer risk factors in Asian ETS studies. Most studies have focused on fuel type. Kerosene was specifically examined in three studies. All three found positive associations--CHAN and LAMW for kerosene cooking, and SHIM for kerosene heating--but none of the associations were statistically significant, and the SHIM relationship held only for adult and not for childhood exposure. Five studies specifically examined coal. GENG evaluated use of coal for cooking and found a significant positive association. Use of coal for household cooking or heating prior to adulthood is significantly associated with lung cancer in WU's study of U.S. residents, but

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no results for adulthood are mentioned. Recent charcoal stove use showed a positive (OR = 1.7) but not significant association in SHIM. Separate analyses of five coal-burning devices and two non-coal-burning devices by WUWI found positive although not always significant associations for the coal burners. In contrast, SOBU found no association between use of unventilated heating devices--including mostly kerosene and coal-fueled types but also some wood and gas burners--and lung cancer (OR = 0.94 for use at age 15, 1.09 at age 30, 1.07 at present). Results for wood or straw cooking were specifically reported in three studies. SOBU found a significant association for use of wood or straw at age 30 (OR = 1.89; 95% C.I. = 1.16, 3.06) but only a weak relationship at age 15. GAO found no association with current use of wood for cooking (OR = 1.0; 95% C.I. = 0.6, 1.8), and WUWI mentions that years of household heating with wood, central heating, and coal showed nonsignificant trends (negative, negative, and positive, respectively).

Overall, studies that examined heating and cooking fuels generally found evidence of an association with lung cancer for at least one fuel, which was usually but not always statistically significant. Such relationships appeared most consistently for use of coal and most prominently in WUWI and LIU. Neither study found a significant association between ETS and lung cancer, nor did either address whether coal use was associated with ETS exposure. The presence of non-ETS sources of smoke within households, however, may effectively mask detection of any effect due to ETS (as noted by the authors of WUWI). Evidence of effects of other fuel types and devices is more difficult to evaluate, particularly because many studies do not report results for these factors, but kerosene-fueled devices seem worthy of further investigation.

5.4.5. Cooking With Oil

Cooking with oil was examined by GAO and WUWI, both conducted in China, with positive associations for deep-frying (OR ranges of 1.5-1.9 and 1.2-2.1, respectively, both increasing with frequency of cooking with oil). GAO also reports positive findings for stir-frying, boiling (which in this population often entails addition of oil to the water), and smokiness during cooking and found that most of these effects seemed specific for users of rapeseed oil. These results may apply to other populations where stir-frying and certain other methods of cooking with oil are common. Neither study, however, addressed whether use of cooking with oil is correlated with ETS exposure.

5.4.6. Occupation

Seven studies investigated selected occupational factors, with five reporting positive outcomes for one or more occupational variables. The outcomes, however, are somewhat inconsistent. SHIM found a strong and significant relationship with occupational metal exposure

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(OR = 4.8) and a nonsignificant one with coal, stone, cement, asbestos, or ceramic exposure, while WUWI found significant positive relationships for metal smelters (OR = 1.5), occupational coal dust (OR = 1.5), and fuel smoke (OR = 1.6) exposure. Textile work is positively associated with lung cancer in KABA and negatively associated with lung cancer in WUWI. BUFF divided occupations into nine categories plus housewife and found eight positive and one negative associations relative to housewives, but only one ("clerical") is significant. GAO, on the other hand, found no association with any of six occupational categories, while GENG found a significant association for an occupational exposure variable that encompassed textiles, asbestos, benzene, and unnamed other substances (OR = 3.1; 95% C.I. = 1.58, 6.02). WU reported "no association between any occupation or occupational category," although there was a nonsignificant excess among cooks and beauticians. Finally, BUTL(Coh) found an increased RR for wives whose husbands worked in blue collar jobs (> 4; never-smoker). HIRA(Coh) did not present findings for husband's occupation as a risk factor independently but reported that adjustment for this factor did not alter the study's ETS results. Few studies attempted to adjust ETS findings for occupational factors--SHIM found only modest effects of such adjustment for occupational metal exposure, despite an apparent strong independent effect for this factor, and GENG found only minimal effect of occupational exposure on active smoking results but did no adjustment of ETS results. Overall, multiple comparisons, other factors (e.g., socioeconomic status, age), and the rarity of most specific occupational exposure sources probably account for the inconsistent role of occupation in these studies.

5.4.7. Dietary Factors

Investigations related to diet have been reported in nine of the ETS studies, with mixed outcomes. The fundamental difficulty lies in obtaining accurate individual values for key nutrients of interest, such as β-carotene. The relatively modest size of most ETS study populations adds further uncertainty in attempts to detect and assess any dietary effect that, if present, is likely to be small. In those studies where dietary data were collected and adjusted for in the analysis of ETS, diet has had no significant effect. Nevertheless, diet has received attention in the literature as a possible explanatory factor in the observed association between ETS exposure and lung cancer occurrence (e.g., Koo, 1988; Koo et al., 1988; Sidney et al., 1989; Butler, 1990, 1991; Marchand et al., 1991); therefore, a more detailed and specific discussion is provided in this section.

Diet is of interest for a potential protective effect against lung cancer. If nonsmokers unexposed to passive smoke have a lower incidence of spontaneous (unrelated to tobacco smoke) lung cancer incidence due to a protective diet, then the effect would be upward bias in the RR for

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ETS. However, for diet to *explain* fully the significant association of ETS exposure in Greece, Hong Kong, Japan, and the United States, which differ by diet as well as other lifestyle characteristics, it would need to be shown that in *each* country: (1) there is a diet protective against lung cancer from ETS exposure, (2) diet is inversely associated with ETS exposure, and (3) the association is strong enough to produce the observed relationship between ETS and lung cancer. Diet may modify the magnitude of any lung cancer risk from ETS (conceivably increase or decrease risk, depending on dietary components), but that would not affect whether ETS is a lung carcinogen.

The literature on the effect of diet on lung cancer is not consistent or conclusive, but taken altogether there may be a protective effect from a diet high in β-carotene, vegetables, and possibly fruits. Also, there is some evidence that low consumption of these substances may correlate with increased ETS exposure, although not necessarily for all study areas. The calculations made by Marchand et al. (1991) and Butler (1990, 1991) are largely conjectural, being based only on *assumed* data. Therefore, we examined the passive smoking studies themselves for empirical evidence on the effect of diet and whether it may affect ETS results.

It was found that nine of the studies have data on diet, although only five of them use a form of analysis that assesses the impact of diet on the ETS association. None of those five studies--CORR, HIRA(Coh), KALA, SHIM, and SVEN--found that diet made a significant difference. In the four studies where data on diet were collected but not controlled for in the analysis of ETS, three (GAO, KOO, and WUWI) are from East Asia and one (WU) is from the United States. Koo (1988), who found strong protective effects for a number of foods, has been one of the main proponents of the idea that diet may explain the passive smoking lung cancer effect. To our knowledge, however, she has not published a calculation examining that conjecture in her own study where data were collected on ETS subjects. In WU, a protective effect of β-carotene was found, but the data include a high percentage of smokers (80% of the cases for adenocarcinoma, 86% for squamous cell), and the number of never-smokers is small. In recent correspondence concerning the large FONT study, its authors state that "mean daily intake of beta-carotene does not significantly differ between study subjects whose spouse smoked and those whose spouse never smoked" (Fontham et al., 1992).

The equivocal state of the literature regarding the effect of diet on lung cancer is also apparent in the nine ETS studies that include dietary factors, summarized in Table 5-15. Note that GAO found an adverse effect from β-carotene. HIRA and KOO found opposite effects from fish while SHIM found no effect. Fruit was found to be protective by KALA and KOO but adverse by SHIM and WUWI. Retinol (based on consumption of eggs and dairy products) was found to be protective by KOO but adverse by GAO and WUWI.

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Table 5-15. Dietary effects in passive smoking studies of lung cancer in females

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
CORR[2]	2.07	Carotene Vitamin A	No data given No data given				Never-smokers. Carotene and total vitamin A were examined. "Except for gender, age, and study area, no confounding was detected."
GAO	1.19	Carotene rich Retinol rich Vitamin A index	1.0 1.0 1.0	1.0 1.1 1.6[3]	1.3 1.0 1.2	2.0[3] 1.1 2.0[3]	Patterns were similar for smokers and nonsmokers. Passive RR was not adjusted for diet, possibly because the trends were the opposite of those in the literature.
HIRA[4]	1.53	Green-yellow veg. Fish Meat Milk Soy paste soup	- - - - -	1.0[5] 1.0 1.0 1.0 1.0	- - - - -	0.86[6] 1.87[3] 0.62 1.30 0.93	Never-smokers. Lung cancer risks for wives whose husbands were former smokers plus 1-19 cig./day smokers and 20+ cig./day smokers relative to never-smokers were 1.50 and 1.79 when adjusted for wives' age (Hirayama, 1984). They ranged from 1.53 to 1.69 and 1.66 to 1.91 when adjusted for wives' age, husband's occupation, and each of the various dietary factors.
KALA	1.92	β-carotene Vegetables Fruits Vitamin C Retinol (preformed)	1.0 1.0 1.0 1.0 1.0	- - - - -	- - - - -	1.01 1.09 0.33[3] 0.67 1.31	Never-smokers. Controlled for age, years of schooling, interviewer, and total energy intake. No confounding was observed between the passive smoking effect and the effect of fruits, or between that of fruits and that of vegetables. Passive risk increased to 2.11 when adjusted for fruit consumption.

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Table 5-15. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
KOO[7]	1.55	Leafy green veg.	-	1.0	0.49	0.49	Never-smokers. Values are adjusted for age, numbers of live births, and schooling. Diet items are selected to compare with those in other studies. No calculation is shown of confounding effect of diet on the passive smoking risk either in Koo et al. (1987), Koo (1988), Koo et al. (1988), or Koo (1989). Fresh fruit, vitamin C, fresh fish, and retinol showed statistically significant trends.
		Carrots	-	1.0	1.31	0.51	
		β-carotene	-	1.0	0.73	0.73	
		Fresh fruit	-	1.0	0.81	0.42	
		Vitamin C	-	1.0	0.55	0.47	
		Fresh fish	-	1.0	0.46	0.35	
		Smoked/cured meat/poultry	-	1.0	0.82	0.92	
		Milk	-	1.0	1.66	0.92	
		Retinol	-	1.0	0.55	0.42	
SHIM	1.08	Green-yellow veg.	-	1.0[8]	-	0.9[8]	Never-smokers. No dose response was found. No difference between cases and controls was found regarding intake of green-yellow vegetables.
		Fruit	-	1.0	-	1.2	
		Milk	-	1.0	-	1.0	
		Fish, pork, or lamb	-	1.0	-	1.0	
		Chicken	-	1.0	-	0.7	
SVEN	1.26	Carrots	1.0[9]	0.7[10]	-	0.6[3,11]	Adjusted for age, smoking, cumulative Rn exposure and municipality. The inclusion of carrot consumption in the regression model "had only a slight effect on the risk estimates of the other exposure variables." See Svensson (1988).

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Table 5-15. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
WU	1.41	β-carotene	1.0	0.52	0.32	0.40[3]	For adenocarcinoma. Risks of 0.67, 1.0, and 0.63, high calf versus low calf, were observed for β-carotene, preformed vitamin A, and dairy and eggs for squamous cell carcinoma. Adjusted for cigarettes smoked per day. No adjustment is shown to the passive risk for diet.
		Preformed Vit. A	1.0	0.92	0.50	0.83	
		Dairy products and eggs	1.0	0.82	0.63[3]	0.37[3]	
WUWI	0.79	Vegetables					Adjusted for age, education, personal smoking, and study area. Eight variables other than smoking were thought to have a significant effect on lung cancer risk. Diet variables were not included in this list, and no adjustment to the passive risk was made for them.
		high-carotene	1.0	1.1	1.0	0.9	
		low-carotene	1.0	1.0	1.0	0.8	
		Fresh fruit	1.0	1.0	1.4[3]	1.5[3]	
		Animal protein	1.0	1.6[3]	1.6[3]	2.3[3]	

[1]From Table 5-5.
[2]As reanalyzed by Dalager et al. (1986).
[3]Statistically significant at the p = 0.05 level.
[4]Case-control study nested in Hirayama's cohort study, ages 40-69 only (Hirayama, 1989).
[5]Less than daily.
[6]Daily.
[7]From Koo (1988).
[8]Cutoffs various.
[9]Less than once per week.
[10]Once per week.
[11]More than once per week.

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In view of the results summarized in Tables 5-14 and 5-15, the actual data of ETS studies do not support the suspicion that diet introduces a systematic bias in the ETS results. Indeed, it would be difficult to show otherwise. Dietary intake is difficult to assess; dietary habits vary within countries and enormously between countries, making it difficult to attribute any effect on lung cancer to a particular food group; lifestyle characteristics and consumption of food and beverage with possibly an adverse effect may be associated, either positively or negatively, with the food group under consideration. It would, of course, be helpful to identify dietary factors that may affect lung cancer, positively or negatively, because that information could usefully contribute to public health. To affect interpretation of ETS results, however, it would need to be established also that consumption of the dietary factor of interest is highly correlated with ETS exposure in study populations where ETS exposure is linked with increased incidence of lung cancer.

5.4.8. Summary on Potential Modifying Factors

In summary, an examination of six non-ETS factors that may affect lung cancer risk finds none that explains the association between lung cancer and ETS exposure as observed by independent investigators across several countries that vary in social and cultural behavior, diet, and other characteristics. On the other hand, the high levels of indoor air pollution from other sources (e.g., smoky coal) that occur in some parts of China and show statistical associations with lung cancer in the studies of GENG, LIU, and WUWI may mask any ETS effects in those studies.

5.5. ANALYSIS BY TIER AND COUNTRY

In this section, attention is directed to properties of individual studies, including potential sources of bias, that may affect their utility for the assessment of ETS and lung cancer. Studies are assessed based on qualitative as well as statistical evaluation. The studies are qualitatively reviewed in Appendix A and categorized into "tiers" within country. Studies are individually scored according to items in eight categories. Study scores are then implemented in a numerical scheme to classify each study into one of four tiers according to that study's assessed utility for hazard identification of ETS. Tier 1 studies are those of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. Tier 4 is reserved for studies we would exclude from analysis for ETS, for various reasons specified in the text. In the statistical analysis presented in this section, the summary RR for each country is recalculated for studies in Tier 1 alone and for Tiers 1-2, 1-3, and 1-4 (the last category corresponds to the combined analysis shown in

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Table 5-9) by country. This exercise provides some idea of the extent to which the summary RR for a country depends on the choice of studies.

The assignment of studies to tiers is shown in Table 5-16. Overall, 5 studies are in the highest tier, while 15, 5, and 5 studies are in Tiers 2, 3, and 4, respectively (KATA was not assigned to a tier). Studies in Tier 4 are not recommended for the objectives of this report. The statistical weight for Tiers 1, 2, and 3 pooled together for each country is shown in Table 5-9 as a percentage of the total for corresponding tiers over all countries. Emphasis on studies through Tier 2 or through Tier 3 is somewhat arbitrary. Although studies in Tier 1 are judged to be of the highest utility, exclusive attention to Tier 1 would eliminate considerable epidemiologic data because only 16% of the studies are in Tier 1. Excluding Tier 4 leaves the choices to either all studies through Tier 2 or through Tier 3. GAO is the only study in China that was not placed in Tier 4, but there is little basis to assume that this single study from Shanghai should be representative of a vast country like China.

Table 5-17 presents adjusted relative risk estimates, 90% confidence intervals, and significance levels (one-sided) from studies pooled by country and by tier. The pooled relative risks do not decrease as the results from studies in Tier 2 and Tier 3 are combined with those from Tier 1, with two exceptions: In the United States, the pooled estimate changes from 1.28 to 1.22 to 1.19 when Tier 2 and Tier 3 studies are added, respectively, and in Western Europe, the pooled estimate changes from 1.21 to 1.17 when Tier 2 studies are added. The pooled estimates for studies through Tier 2 are statistically significant at $p = 0.02$ (one-tailed) in Greece, Hong Kong, Japan, and the United States; Western Europe is the exception ($p = 0.22$). The same statement holds with Tier 2 replaced by Tier 3, except that China includes one study at $p = 0.18$. The relative risk results from all four Western European studies (RR = 1.17) is virtually the same for all U.S. studies (RR = 1.19), but with less power that value is not significant for Western Europe. The similarity of outcomes is also interesting, however, because Western Europe is probably more similar to the United States than the other countries.

Analysis by tiers provides a methodology for weighting studies according to their utility for hazard identification of ETS. It allows one to emphasize those studies thought to provide better data for analysis of an ETS effect. The addition of studies of lower utility to the analysis, such as inclusion of Tier 3 studies with those from Tiers 1 and 2, has a small effect on the relative risk estimate but both increases its statistical significance and narrows its confidence interval. In view of that outcome and the results and discussion in Section 5.4, this analysis finds little to indicate confounding or bias in studies through Tier 3 (which include all studies in the United States). In summary, it is concluded that the association of ETS and lung cancer observed from

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Table 5-16. Classification of studies by tier

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
Greece	KALA	X			
Greece	TRIC			X	
Hong Kong	KOO	X			
Hong Kong	LAMT		X		
Hong Kong	LAMW			X	
Hong Kong	CHAN				X
Japan	AKIB		X		
Japan	HIRA(Coh)		X		
Japan	SHIM		X		
Japan	SOBU		X		
Japan	INOU				X
United States	FONT	X			
United States	BUTL(Coh)		X		
United States	GARF		X		
United States	HUMB		X		
United States	JANE		X		
United States	WU		X		
United States	BROW		X		
United States	BUFF			X	
United States	CORR		X		
United States	GARF(Coh)			X	
United States	KABA		X		

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Table 5-16. (continued)

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
W. Europe					
Scotland	HOLE(Coh)	X			
Sweden	PERS	X			
Sweden	SVEN		X		
England	LEE		X		
China	GAO			X	
China	GENG				X
China	LIU				X
China	WUWI				X

the analysis of 30 epidemiologic studies in eight different countries is not due to chance alone and is not attributable to bias or confounding.

5.6. CONCLUSIONS FOR HAZARD IDENTIFICATION

5.6.1. Criteria for Causality

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria [that] must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

As demonstrated in the preceding sections, the overall results observed in the 30 epidemiologic studies are not attributable to chance and the association between ETS and lung cancer is not explained by bias or confounding.

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Table 5-17. Summary data interpretation by tiers within country[1]

Through Tier[2]	Relative weight[3] (%)	Country[4]	Studies added	RR	Confidence interval 90%	P-value effect
1		Greece	KALA	1.92	(1.13, 3.23)	0.02
2	4	Greece	---	1.92	(1.13, 3.23)	0.02
3	6	Greece	TRIC	2.01	(1.42, 2.84)	0.0005
4		Greece	---	2.01	(1.42, 2.84)	0.0005
1		Hong Kong	KOO	1.54	(0.98, 2.43)	0.06
2	16	Hong Kong	LAMT	1.61	(1.25, 2.07)	0.0009
3	14	Hong Kong	LAMW	1.75	(1.39, 2.19)	0.00002
4		Hong Kong	CHAN	1.48	(1.21, 1.81)	0.0008
1		Japan	---	---	---	---
2	30	Japan	AKIB, HIRA(Coh), SHIM, SOBU	1.39	(1.16, 1.66)	0.001
3	23	Japan	---	1.39	(1.16, 1.66)	0.001
4		Japan	INOU	1.41	(1.18, 1.69)	0.0007
1		United States	FONT	1.28	(1.03, 1.60)	0.03
2	41	United States	BUTL(Coh), CORR, GARF, HUMB, JANE, KABA, WU	1.22	(1.04, 1.42)	0.02
3	43	United States	BROW, BUFF, GARF(Coh)	1.19	(1.04, 1.35)	0.02
4		United States	---	1.19	(1.04, 1.35)	0.02
1		W. Europe	HOLE(Coh), PERS	1.21	(0.79, 1.90)	0.24
2	9	W. Europe	SVEN, LEE	1.17	(0.85, 1.64)	0.22
3	7	W. Europe	---	1.17	(0.85, 1.64)	0.22
4		W. Europe	---	1.17	(0.85, 1.64)	0.22
1		China	---	---	---	---
2	0	China	---	---	---	---
3	7	China	GAO	1.19	(0.87, 1.62)	0.18
4		China	GENG, LIU, WUWI	0.95	(0.81, 1.12)	0.70

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Table 5-17. (continued)

[1]Use of Tiers 1 through 2 or Tiers 1 through 3, both shown in boldface, is recommended. Tier 4 is *not* recommended.
[2]Each line contains the studies in the previous tiers plus those added.
[3]Percentage of total weight by country for Tiers 1 through 2 or 1 through 3.
[4]Western Europe consists of England, Scotland, and Sweden.

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Below, the evidence for a causal association between ETS and lung cancer is evaluated according to seven specific criteria for causality developed by an EPA workshop to supplement the *Guidelines* (U.S. EPA, 1989). These criteria are similar to the original and classical recommendations of Hill (1953, 1965). The seven recommended (but not official) criteria from the EPA workshop, which vary between essential and desirable, are listed below (U.S. EPA, 1989).

> A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of these actually establishes causality; actual proof is rarely attainable when dealing with environmental carcinogens. The absence of any one or even several of the others does not prevent a causal interpretation. Only the first criterion (temporal relationship) is essential to a causal relationship: with that exception, none of the criteria should be considered as either necessary or sufficient in itself. The first six criteria apply to an individual study. The last criterion (coherence) applies to a consideration of all evidence in the entire body of knowledge.

1. Temporal relationship: The disease occurs within a biologically reasonable timeframe after the initial exposure to account for the specific health effect.

2. Consistency: When compared to several independent studies of a similar exposure in different populations, the study in question demonstrates a similar association which persists despite differing circumstances. This usually constitutes strong evidence for a causal interpretation (assuming the same bias or confounding is not also duplicated across studies).

3. Strength of association: The greater the estimate of risk and the more precise, the more credible the causal association.

4. Dose-response or biologic gradient: An increase in the measure of effect is correlated positively with an increase in the exposure or estimated dose. If present, this characteristic should be weighted heavily in considering causality. However, the absence of a dose-response relationship should not be construed by itself as evidence of a lack of a causal relationship.

5. Specificity of the association: In the study in question, if a single exposure is associated with an excess risk of one or more cancers also found in other studies, it increases the likelihood of a causal interpretation.

6. Biological plausibility: The association makes sense in terms of biological knowledge. Information from toxicology, pharmacokinetics, genotoxicity, and in vitro studies should be considered.

7. Coherence: Coherence exists when a cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease. A proposed association that conflicted with existing knowledge would have to be examined with particular care. (This criterion has been called "collateral evidence" previously.)

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5.6.2. Assessment of Causality

We consider the extent to which the criteria for causality are satisfied for the ETS studies. Regarding *temporal relationship*, ETS exposure classification is typically based on the marital history of a subject, which varies, or on the status at the beginning of a prospective cohort study. Very few studies up through Tier 3 considered current exposure status only (see Appendix A), so some history of ETS exposure is largely the rule for ETS-exposed subjects. Analysis of data by exposure level in Section 5.3.3 indicates increased relative risk with exposure level, which supports the temporal relationship.

If ETS causes lung cancer, then the true relative risk is small for detection by epidemiologic standards and may differ between countries as well. However, by considering the totality of the evidence, it is determined that the large accumulation of epidemiologic evidence from independent sources in different locales and circumstances, under actual exposure conditions, is adequate for conclusiveness. Having accounted for variable study size, adjusted for a possible systematic spousal bias due to smoker misclassification, and considered potential bias, confounding, and other sources of uncertainty on a study-by-study basis, *consistency* of a significant association is clearly evident for the summary statistical measures for Tiers 1 through 2 and 1 through 3 in Greece, Hong Kong, Japan, and the United States. The combined countries from Western Europe are similar in outcome to the United States, although significance is not attained. There is too much obscurity and uncertainty attached to the studies in China for adequate data interpretation.

The relative risks for each country are obtained by pooling estimates from the epidemiologic studies conducted in the country. The *strength of association* is limited by the true value of the relative risk, which is small. Statistical significance is attained, however, for the pooled studies of the United States and most other countries. The data were obtained from actual conditions of environmental exposure; therefore, imprecision is not increased by extrapolation of results from atypically high exposure concentrations, a common situation in risk analysis. Additionally, all studies were individually corrected for systematic bias from smoker misclassification at the outset, and qualitative characteristics of the studies were carefully reviewed to emphasize the results from the studies with higher utility for the objectives of this report. The outcome for the United States is heavily influenced by the large National Cancer Institute study (FONT) that was specifically designed and executed to avoid methodological problems that might undermine the accuracy or precision of the results.

Of the 14 studies reporting a test for upward trend, 10 are statistically significant at 0.05 (see Table 5-12) which would occur by chance alone with probability less than 10^{-9}. This

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evidence of *dose response* is very supportive of a causal interpretation because it would be an unlikely result of any operative sources of bias or confounding.

Specificity does not apply to ETS. Although ETS has been assessed for the same endpoint (lung cancer) in all studies, the occurrence of lung cancer is not specific to ETS exposure. Data on histological cell type are not conclusive. The study by Fontham and colleagues (1991) suggests that adenocarcinoma may be more strongly related to ETS exposure than other cell types. Adenocarcinoma, however, does not appear to be etiologically specific to ETS.

Biomarkers such as cotinine/creatinine levels clearly indicate that ETS is taken up by the lungs of nonsmokers (see Chapter 3). The similarity of carcinogens identified in sidestream and mainstream smoke, along with the established causal relationship between lung cancer and smoking in humans with high relative risks and dose-response relationships in four different lung cell types down to low exposure levels, provide *biological plausibility* that ETS is also a lung carcinogen (Chapter 4). In addition, animal models and genotoxicity assays provide corroborating evidence for the carcinogenic potential of ETS (Chapter 4). The epidemiologic data provide independent empirical verification of the anticipated risk of lung cancer from passive smoking and also an estimate of the increased risk of lung cancer to never-smoking women. The *coherence* of results from these three approaches and the lack of significant arguments to the contrary strongly support causality as an explanation of the observed association between ETS exposure and lung cancer.

5.6.3. Conclusion

Based on the assessment of all the evidence considered in Chapters 3, 4, and 5 of this report and in accordance with the EPA *Guidelines* and the causality criteria above for interpretation of human data, this report concludes that ETS is a Group A human carcinogen, the EPA classification "used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer" (U.S. EPA, 1986a).

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6. POPULATION RISK OF LUNG CANCER FROM PASSIVE SMOKING

6.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that environmental tobacco smoke (ETS) exposure is causally associated with lung cancer. If an effect is large enough to detect in epidemiologic studies investigating the consequences of ETS exposure at common exposure levels, the individual risk associated with exposure is considered to be high compared with most environmental contaminants assessed. Of course, the number of lung cancer deaths attributable to ETS exposure for a whole population, such as the United States, depends on the number of persons exposed as well as the individual risk. Studies of cotinine/creatinine concentrations in nonsmokers indicate that ETS is virtually ubiquitous. For example, in urinary bioassays of 663 nonsmokers, Cummings et al. (1990) found that over 90% had detectable levels of cotinine. Among the 161 subjects who reported no recent exposure to ETS, the prevalence of detectable cotinine was still about 80%. Although the average cotinine level for all those tested may be below the average for subjects exposed to spousal ETS, as studied in this report, it indicates uptake of ETS to some extent by a large majority of nonsmokers (see also Chapter 3). Consequently, exposure to ETS is a public health issue that needs to be considered from a national perspective.

This chapter derives U.S. lung cancer mortality estimates for female and male never-smokers and long-term (5+ years) former smokers. Section 6.2 discusses prior approaches to estimating U.S. population risk. Section 6.3 presents this report's estimates. First, the parameters and formulae used are defined (Section 6.3.2), and then lung cancer mortality estimates are calculated from two different data sets and confidence and sources of uncertainty in the estimates are discussed. Section 6.3.3 derives estimates based on the combined relative risk estimates of the 11 U.S. studies from Chapter 5. Section 6.3.4 bases its estimates on the data from the single largest U.S. study, that of Fontham et al. (1991). Finally, Section 6.3.5 discusses the sensitivity of the estimates to changes in various parameter values. ETS-attributable lung cancer mortality rates (LCMR) for each of the individual studies from Chapter 5 are presented in Appendix C.

6.2. PRIOR APPROACHES TO ESTIMATION OF POPULATION RISK

Several authors have estimated the population risk of lung cancer from exposure to ETS. Two approaches have been used almost exclusively. One approach analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report; the other estimates a dose-response relationship for ETS exposure extrapolated from active smoking, based on "cigarette-equivalents" determined from a surrogate measure of exposure common to

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passive and active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

6.2.1. Examples Using Epidemiologic Data

The National Research Council report (NRC, 1986) is a good example of the epidemiologic approach. An overall estimate of relative risk (RR) of lung cancer for never-smokers exposed to both spousal smoking and background ETS versus those exposed only to background ETS is obtained by statistical summary across all available studies. Two "corrections" are then made to the estimate of RR to correct for the two sources of systematic bias. The first correction accounts for expected upward bias from former smokers and current smokers who may be misclassified as never-smokers; this correction results in a decrease in the RR estimate. The second correction is an upward adjustment to the RR taking into account the risk from background exposure to ETS (experienced by a never-smoker whether married to a smoker or not) to obtain estimates of the excess lung cancer risk from all sources of ETS exposure (spousal smoking and background ETS) relative to the risk in an ETS-free environment. Population risk can then be characterized by estimating the annual number of lung cancer deaths among never-smokers attributable to all sources of ETS exposure. This calculation requires the final corrected estimates of RR (one for background ETS only and one for background plus spousal smoking), the annual number of lung cancer deaths (LCDs) from all causes in the population assessed (e.g., never-smokers of age 35 and over), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to some average background level of ETS; although, in fact, the population contains some individuals with high exposure and others with virtually no exposure.

The NRC report combines data for female and male never-smokers to obtain an overall observed RR estimate of 1.34 (95% confidence interval [C.I.] = 1.18, 1.53), but this estimate is most heavily influenced by the abundant female data. (The female data alone generate a combined RR estimate of 1.32 [95% C.I. = 1.18, 1.52], while the male data produce an RR estimate of 1.62 [95% C.I. = 0.99, 2.64].) To adjust for potential misclassification bias, the NRC uses the construct of Wald and coworkers. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. After correcting the overall observed RR estimate of 1.34 downward for an expected positive (upward) bias from smoker misclassification, the NRC concludes that the relative risk is about 1.25, and probably lies between 1.15 and 1.35. Correction for background sources (i.e., nonspousal sources of ETS) increases the NRC estimate of RR for an "exposed" person (i.e., exposed to ETS from spousal smoking) to 1.42 (range of 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS exposure instead of relative to nonspousal sources of ETS. Under this redefinition, the RR for an

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"unexposed" person (i.e., unexposed to spousal ETS) versus a truly unexposed person (i.e., in a zero-ETS environment) becomes 1.14 (range of 1.08 to 1.21). The NRC report further estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C); these estimates, however, are based on RRs corrected for background ETS but not for smoker misclassification. Applying these percentages to estimates of 6,500 LCDs in never-smoking women and 3,000 LCDs in never-smoking men in 1988 (American Cancer Society, personal communication), the number attributable to ETS exposure is 1,365 and 600, respectively, for a total of about 2,000 LCDs among never-smokers of both sexes.

Robins (NRC, 1986, Appendix D [included in the NRC report but neither endorsed nor rejected by the committee]) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant assumptions clearly stated. A related article by Robins et al. (1989) contains most of the same information. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: (1) correction of relative risk for background exposure to ETS independent of age, and (2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. In this method, Robins uses a weighted average RR of 1.3. After correcting this RR for background ETS exposure, age-adjusted population-attributable risks are calculated for females and males separately. Adjusting Robins' results to 6,500 annual LCDs in female never-smokers and 3,000 LCDs in male never-smokers, for comparison purposes, yields estimates of 1,870 female LCDs and 470 male LCDs attributable to ETS. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. Again, adjusting Robins' estimates to 6,500 female LCDs and 3,000 male LCDs, the range of excess LCDs attributable to ETS is 1,650 to 2,990 for never-smoking females and 420 to 1,120 for never-smoking males. Method 3 is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

The Centers for Disease Control (CDC) has published an estimate of 3,825 (2,495 female and 1,330 male) deaths in nonsmokers from lung cancer attributable to passive smoking for the year 1988 (CDC, 1991a), with reference to the NRC report of 1986. Those figures are the midrange of values for males and females from method 2 of Robins in Appendix D of the NRC report (NRC, 1986).

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time that the reports of the Surgeon General and NRC appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report, except for omission of one cohort study (Gillis et al., 1984), and inclusion of Wu et al.

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(1985), the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. = 1.1, 1.5). When the results are combined for high-exposure categories, the overall relative risk estimate is 1.7 (1.4, 2.1).

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and Surgeon General's reports of 1986 (NRC, 1986; U.S. DHHS, 1986). Like the NRC report, the epidemiologic data for both women and men are considered, for which Wells provides separate estimates of overall relative risk and attributable risk. Wells calculates an overall relative risk of 1.44 (95% C.I. = 1.26, 1.66) for females and 2.1 (1.3, 3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ever-smokers is assumed to be 5% (compared to 7% for Wald et al.). Rates are corrected for background exposure to ETS, except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins, NRC, Appendix D). The calculation of population-attributable risk applies to former smokers as well as never-smokers, which is a departure from Wald et al. and the NRC report. The annual number of LCDs attributable to ETS in the United States is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be the best current estimate (Wells, 1988). (In addition to the estimates of ETS-attributable LCDs, Wells uses the epidemiological approach to derive estimates of ETS-attributable deaths from other cancers--11,000--and from heart disease--32,000.)

Saracci and Riboli (1989), of the International Agency for Research on Cancer (IARC), review the evidence from the 3 cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. with respect to the exclusion of studies, and add only one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (95% C.I. = 1.20, 1.53), is about the same as that reported by the NRC, 1.34 (1.18, 1.53). It is not reported how the overall relative risk was calculated.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. One method is based on epidemiologic data, but, unlike the previous examples, Repace and Lowrey use a study comparing Seventh-Day Adventists (SDAs) (Phillips et al., 1980a,b) with a demographically and educationally matched group of non-SDAs who are also never-smokers to obtain estimates of the relative risk of lung cancer mortality, in what they describe as a "phenomenological" approach. The SDA/non-SDA comparison provides a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the other epidemiologic studies. It also serves as an independent source of data and an alternative approach

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for comparison. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The basis for comparison of the two groups is the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA group due to differences in lifestyle. Relatively few SDAs smoke, so an SDA never-smoker is probably less likely to be exposed at home by a smoking spouse, in the workplace, or elsewhere, if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. (1980 a,b) reported that the non-SDA cohort experienced an average LCMR equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in LCMR for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million never-smokers in the United States in 1979 to obtain the number of LCDs attributable to ETS annually. The result, 4,665, corresponds to a risk rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1,000 people exposed. The second method described by Repace and Lowrey is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

Wigle et al. (1987) apply the epidemiologic evidence from the SDA/non-SDA study (Phillips et al., 1980a,b) to obtain estimates of the number of LCDs in never-smokers due to ETS in the population of Canada. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and the age-specific rates of death from lung cancer attributable to ETS estimated by Repace and Lowrey (1985). A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually.

6.2.2. Examples Based on Cigarette-Equivalents

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after extrapolation of the curve to lower doses and conversion of ETS exposure into an "equivalent" exposure from active smoking, determined from a surrogate measure of exposure common to passive and active smoking. Relative cotinine concentrations in body fluids (urine, blood, or saliva) of smokers versus nonsmokers and tobacco smoke particulates in sidestream smoke (SS) and mainstream smoke (MS) have commonly been used for this purpose. The lung cancer risk of ETS is assumed to equal the risk from active smoking at the rate determined by the cigarette-equivalents. For example, suppose the average cotinine concentration in exposed never-smokers is 1% of the average value found in people who smoke 30 cigarettes per day. The lung cancer risk for a smoker of (0.01)30 =

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0.3 cigarettes per day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both. This assumption may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physicochemical properties in general; the lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages. Active and passive smoking also differ in characteristics of intake; for example, intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation, which may affect deposition and systemic distribution of various tobacco smoke components as well (see Sections 3.2 and 3.3.2).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, conclude that "the differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989) states, "Lacking knowledge of which substances are responsible for the well-established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The Surgeon General's report devotes a three-page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. DHHS, 1986). It concludes that "these limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." (On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well characterized. Recent literature raises some questions on this issue [Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a,b; Whittemore, 1988].)

Citing cigarette-equivalents calculated in other sources, Vutuc (1984) assumes a range of 0.1 to 1.0 cigarettes per day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Döll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cigarettes per day give a range in relative risk from 1.03 to 1.36. The author concludes that "as it applies to passive

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smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. If the number of LCDs among never-smokers in the United States in 1988 is about 6,500 females and 3,000 males (personal communication from the American Cancer Society), then the number of LCDs in never-smokers attributable to ETS is estimated to range from 240 to 2,020 (140 to 1,380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among never-smokers in the United States. These estimates are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as an alternative to their "phenomenological" approach discussed in Section 6.2.1. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-6} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that inhaled tobacco tar poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (never-smokers and former smokers) are attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including former smokers).

Method 3 of Robins (NRC, 1986, Appendix D--again, included in the NRC report but not specifically endorsed by the committee) extrapolates from data on active smoking, along with several assumptions. Applying his results to 6,500 females and 3,000 males, the range of excess LCDs in never-smokers due to ETS is 550 to 2,940 for females and 153 to 1,090 for males.

Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death

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from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4,000+ deaths per year due to passive smoking, is for all causes of death, not just LCDs.

Arundel et al. (1987) attributes only five LCDs among female never-smokers to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6,500 females and 3,000 males). The expected lung cancer risk for never-smokers is estimated by downward extrapolation of the lung cancer risk per mg of particulate ETS exposure for current smokers. The authors' premise is that the lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase (e.g., see Wells, 1991).

6.3. THIS REPORT'S ESTIMATES OF LUNG CANCER MORTALITY ATTRIBUTABLE TO ETS IN THE UNITED STATES

6.3.1. Introduction and Background

This report uses the epidemiologic approach because of the abundance of human data from actual environmental exposures. Furthermore, the assumptions are fewer and more valid than for the cigarette-equivalents approach. The report generally follows the epidemiologic methodology used by the NRC (NRC, 1986) and others (Section 6.2.1), with three important differences. The first difference is that the NRC combined the data on females and males for its summary relative risk estimate. This report uses only the data on females because there are likely to be true sex-based differences in relative risk due to differences in exposure to background ETS and differences in background (i.e., non-tobacco-smoke-related) lung cancer risk. Furthermore, the vast majority of the data are for females. The second difference is that the NRC combined study estimates of relative risk across countries for its summary relative risk estimate; this report combines relative risk estimates only within countries, and then bases the U.S. population risk assessment on the U.S. estimate only. As discussed in Chapter 5, there are apparently true differences in the observed relative risk estimates from different countries, which might reflect lifestyle differences, differences in background lung cancer rates in females, exposure to other indoor air pollutants, and differences in exposure to background levels of ETS. Therefore, for the purposes of U.S. population risk assessment, it is appropriate to use the U.S. studies; in addition, far more studies are currently available so there is less need to combine across countries. The

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third difference is that the NRC corrected its overall estimate of relative risk downward for smoker misclassification bias. In this report, the individual study estimates are corrected for smoker misclassification bias at the outset, i.e., prior to any analysis, using the particular parameters appropriate for each separate study (Appendix B).

The basic NRC model is defined as

$$RR(d_E) = (1 + Z * \beta d_N)/(1 + \beta d_N)$$

where $RR(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS); Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N; and β is the amount of increased risk per unit dose. The equation is only defined for $Z > RR(d_E) > 1$ (see Section 8.3).

The method used here is based on several assumptions: (1) that body cotinine levels in never-smokers are linearly related to ETS exposure; (2) that current ETS exposure is representative of past exposures; and (3) that the excess risk of lung cancer in nonsmokers exposed to ETS is linearly related to the dose absorbed.

Estimates of $RR(d_E)$ for female never-smokers were derived in Chapter 5, where they were corrected for smoker misclassification bias; these are redefined in Section 6.3.2 as RR_2. The relative risk estimates are then adjusted to be applicable to different baseline exposure groups in order to calculate population risks for never-smoking women. In order to extend the analyses to female former smokers and male never- and former smokers, the relative risks are converted to excess or additive risks. The use of additive risks is more appropriate for these groups because of the different baseline lung cancer mortality rates by sex and smoking status (former vs. never).

More specifically, estimates of ETS-attributable population mortality are calculated from female lung cancer mortality rates, which are themselves derived from summary relative risk estimates either from the 11 U.S. studies combined (Section 6.3.3) or from the Fontham et al. (1991) study alone (Section 6.3.4), along with other parameter estimates from prominent sources (Section 6.3.2). The LCMRs in this instance are defined as the number of LCDs in 1985 per 100,000 of the population at risk. The LCMR in U.S. women under age 35 is minuscule, so only persons of age 35 and above are considered at risk. Although these LCMRs are expressed as a mortality rate per 100,000 of the population at risk, as derived they are applicable only to the entire population at risk and not to any fraction thereof that might, for example, have a different average exposure or age distribution.

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The LCMR for the subpopulation and exposure scenario to which the epidemiologic studies apply most directly--never-smoking females exposed to spousal ETS--is estimated first. That estimate is then incremented to include exposure to nonspousal ETS for all never-smoking females. For the ETS-attributable population mortality estimates, these LCMRs are applied to never-smoking males and former smokers at risk, as well as to the females at risk for which the rates were specifically derived. The most reliable component of the total estimate constructed for the United States is the estimate for the female never-smokers exposed to spousal ETS. The other components require additional assumptions, which are described. As the number of assumptions increases, so does the uncertainty of the estimates. Thus, the total estimate of lung cancer risk to U.S. nonsmokers of both sexes is composed of component estimates of varying degrees of certainty.

One might argue that smokers are among those most heavily exposed to ETS, since they are in close proximity to sidestream smoke (the main component of ETS) from their own cigarettes and are also more likely than never-smokers to be exposed to ETS from other smokers. The purpose of this report, however, is to address respiratory health risks from ETS exposure in nonsmokers. In current smokers, the added risk from passive smoking is relatively insignificant compared to the self-inflicted risk from active smoking.

6.3.2. Parameters and Formulae for Attributable Risk

Several parameters and formulae are needed to calculate attributable risk. These are presented in Table 6-1, with the derivations explained below.

The size of the target population, in this case the number of women in the United States of age 35+ in 1985, is denoted by N, with $N = N_1 + N_2$, where N_1 = the number of ever-smokers and N_2 = the number of never-smokers. The total number of LCDs from all sources, T, is apportioned into components from four attributable sources: (1) non-tobacco-smoke-related causes, the background causes that would persist in an environment free of tobacco smoke; (2) background ETS, which refers to all ETS exposure other than that from spousal smoking; (3) spousal ETS; and (4) ever-smoking. The risk from non-tobacco-smoke-related causes (source 1) is a baseline risk (discussed below) assumed to apply equally to the entire target population (never-smokers and ever-smokers alike). The ever-smoking component of attributable risk (source 4) refers to the incremental risk above the baseline in ever-smokers (this report does not partition the incremental risk in ever-smokers further into components due to background ETS and spousal ETS, except for long-term [5+ years] former smokers). The background ETS component (source 2) is the incremental risk above the baseline in all never-smokers from exposure to nonspousal sources of

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Table 6-1. Definition and estimates of relative risk of lung cancer for 11 U.S. studies combined for various exposure sources and baselines; population parameter definitions and estimates used to calculate U.S. population-attributable risk estimates for ETS

DENOMINATOR (Baseline)	NUMERATOR of relative risk			
	All persons	Never-smokers ETS exposure		Current and former smokers
Source of exposure	Non-tobacco-smoke sources of exposure	Background ETS	Background ETS and spousal ETS	Active smoking
	[nt]	[nt]+[ETS_B]	[nt]+[ETS_B]+[ETS_S]	[nt]+[ETS]+[ACT]
[nt]	1	RR_{03} = 1.34	RR_{02} = 1.59[1]	RR_{01} = 13.8
[nt]+[ETS_B]	-	-	RR_2 = 1.19[2]	RR_{11} = 10.3
[nt]+[ETS_B]+[ETS_S]	-	-	-	RR_1 = 9.26[3]

[1]Basic adjustment for background exposure with Z = 1.75.
[2]Pooled value from 11 U.S. studies for never-smoking females.
[3]RR_1 = a weighted average of 11.94 for women active smokers (63.4%) and 4.69 for women former smokers (36.6%) = 9.26.

Definitions and Estimates of Population Parameter Values

N = Total number of women in U.S. (1985) age 35+ = N_1 (ever-smokers) + N_2 (never-smokers) = 25.7 million + 32.3 million = 58 million.
P_1 = Prevalence (proportion) of female ever smokers age 35+ = 0.443.
P_2 = Proportion of NS women exposed to equivalent spousal ETS (plus background ETS) = 0.6.
Z = Ratio of body cotinine levels in (nonsmokers exposed to background ETS plus spousal ETS) to (nonsmokers exposed to background ETS only) = 1.75.
T = Total LCDs in United States in 1985 among women aged 35+ = 38,000.

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ETS. The spousal ETS component (source 3) is the additional incremental risk in never-smokers exposed to spousal smoking.

The calculational formulae also require values for the parameters P_1 (prevalence of ever-smokers), P_2 (proportion of never-smokers exposed to spousal smoking), RR_1 (average lung cancer risk for ever-smokers relative to the average risk for never-smokers in the population), and RR_2 (lung cancer risk of never-smokers exposed to spousal ETS relative to never-smokers not exposed to spousal ETS). Additional parameters (RR_{11}, Z, RR_{01}, RR_{02}, and RR_{03}) are introduced or developed below.

The "baseline" risk is defined as the term in the denominator of a risk ratio. For example, in RR_1 the baseline risk is the lung cancer risk in a population of never-smokers with P_2 exposed to spousal ETS and $1 - P_2$ not exposed to spousal ETS. The conversion of RR_1 to the same baseline risk as RR_2 (the risk of never-smokers not exposed to spousal ETS but still exposed to non-tobacco-smoke-related causes and to background ETS), is given by

$$RR_{11} = RR_1(P_2RR_2 + 1 - P_2). \qquad (6\text{-}1)$$

To convert relative risks to the baseline risk of lung cancer from non-tobacco-smoke-related causes only (i.e., excluding background ETS in the baseline) requires some assumptions. Let RR_{02} denote the conversion of RR_2 to this new baseline. It is assumed that: (1) the excess risk of lung cancer from ETS exposure is proportional to ETS exposure; and (2) the ratio of ETS exposure from spousal smoking plus other sources to exposure from other sources alone, denoted by Z, is known and $Z > RR_2 > 1$. (For the values used in this report, this relation is true. See also the discussion in Section 8.3.) Under these assumptions, $RR_{02} = 1 + \beta Zd_N$ (from Section 6.3.1), or

$$RR_{02} = (Z - 1)/(Z/RR_2 - 1). \qquad (6\text{-}2)$$

Determination of a value for Z from data on cotinine concentrations (or cotinine/creatinine) is discussed below. The conversion of RR_1 to the same zero-ETS baseline risk as RR_{02} follows from multiplying expression (6-1) by RR_{02}/RR_2, i.e.,

$$RR_{01} = RR_1(P_2RR_{02} + (1 - P_2)RR_{02}/RR_2). \qquad (6\text{-}3)$$

The terms RR_{01} and RR_{02} are the lung cancer risks for ever-smokers and for never-smokers exposed to spousal ETS, respectively, relative to the risk for never-smokers in a zero-ETS

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environment. The risk of never-smokers not exposed to spousal ETS (but exposed to background ETS and nonsmoking causes) relative to the zero-ETS baseline risk is

$$RR_{03} = RR_{02}/RR_2. \quad (6\text{-}4)$$

The population-attributable risk of lung cancer in the total population for a source (risk factor) is a ratio. The numerators of the ratios for sources of tobacco smoke are:

current/former active smoking in ever-smokers,
$P_1(RR_{01} - 1)$; (6-5)

background ETS plus spousal ETS in never-smokers exposed to both,
$(1 - P_1)P_2(RR_{02} - 1)$; and (6-6)

background ETS in never-smokers not exposed to spousal ETS,
$(1 - P_1)(1 - P_2)(RR_{02}/RR_2 - 1)$. (6-7)

The denominator for each term is their sum plus one, i.e.,

$$Ex(6\text{-}5) + Ex(6\text{-}6) + Ex(6\text{-}7) + 1 \quad (6\text{-}8)$$

where Ex(6-5) refers to expression (6-5), etc. The population-attributable risk for remaining causes of lung cancer (non-tobacco-smoke-related background causes) is

$$1/Ex(6\text{-}8). \quad (6\text{-}9)$$

Multiplying the population-attributable risk for a source by the total number of LCDs yields the number of LCDs attributable to that source. An alternative and equivalent derivation of the source-attributable LCD estimates can be performed by first calculating LCMRs. LCMRs are obtained for each source as follows:

non-tobacco-smoke-related causes:	$LCMR_{nt} = 10^5 Ex(6\text{-}9)T/N$.
ever-smoking:	$LCMR_{nt}(RR_{01} - 1)$.
spousal ETS:	$LCMR_{nt}(RR_{02} - RR_{03})$.
background ETS:	$LCMR_{nt}(RR_{03} - 1)$.

Then the number of LCDs attributable to a source is estimated by multiplying the LCMR for that source by the total population at risk from that source.

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We now consider parameter values for N, T, P_1, P_2, RR_1, and Z to be used with the value 1.19 for RR_2, the pooled estimate of RR_2 from the 11 U.S. studies (Table 5-17), for the population risk assessment in Section 6.3.3. The value used for RR_2 is then changed to 1.28, the estimate from the Fontham et al. (1991) study in the United States, and a new value of Z is constructed from the cotinine data in that study for the alternative population risk assessment calculations in Section 6.3.4. The female population in 1985 of age 18+ years of age is approximately 92 million (U.S. DHHS, 1989, Chapter 3). Detailed census data by age for 1988 indicate that the proportion of women 35+ years of age in the female population of age 18+ is 0.63 (U.S. Bureau of the Census, 1990). Applying that proportion to the 1985 population gives approximately 58 million women of aged 35+ in 1985, the value used for N. There were approximately 38,000 female LCDs in the United States in 1985 (U.S. DHHS, 1989), which is used as the value for T.

Using figures from the Bureau of the Census and the 1979/80 National Health Interview Survey, Arundel et al. (1987) estimate the number of women of age 35+ by smoking status, obtaining a value of 0.443 as the fraction of ever-smokers. The National Center for Health Statistics (as reported in U.S. DHHS, 1989) provides the proportion of the female population by smoking status (never, former, current) for 1987. When applied to figures from the Bureau of the Census (1990) for the female population by age group available for 1988, the same fractional value (0.443) is obtained. These sources suggest that the proportion of ever-smokers in the female population has been fairly constant between 1980 and 1987, so P_1 will be given the value 0.443. Multiplying N by P_1 gives an estimate of $N_1 = 25.7$ million ever-smokers, leaving $N_2 = 32.3$ million never-smokers.

RR_1 applies to ever-smokers, which consist of current and former smokers. The relative risks of current and former female smokers of age 35+ for the period 1982-1986 are estimated at 11.94 and 4.69, respectively, from data in the American Cancer Society's Cancer Prevention Study II (CPS-II; as reported in U.S. DHHS, 1989). For 1985, the composition of ever-smokers is 63.4% current smokers and 36.6% former smokers (CDC, 1989a). Using those percentages to weight the relative risks for ever-smokers and former smokers gives 9.26, which will be used as the value of RR_1.

The proportion of never-smokers exposed to spousal ETS in epidemiologic studies typically refers to married persons, so we need to consider how to treat unmarried persons as well in order to set a value for P_2. The American Cancer Society's CPS-II (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just never-smokers) are: married, 75.3; divorced, 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female never-smokers, which comprise about 75% of female never-smokers,

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so it is necessary to consider exposure to ETS in the remaining 25% of unmarried female never-smokers.

Cummings (1990) obtained urinary cotinine levels on a total of 663 self-reported never-smokers and former smokers. The cotinine levels were slightly higher in males than in females (9.6 and 8.2 ng/mL, respectively), and slightly more than one-half of the subjects were females. The average cotinine level was 10.7 ng/mL for married subjects if the spouse smoked and 7.6 ng/mL otherwise. The average cotinine levels reported by marital status are: married, 8.3 ng/mL; never married, 10.3 ng/mL; separated, 11.8 ng/mL; widowed, 10.4 ng/mL; and divorced, 9.2 ng/mL. The study, in which 7% of the subjects were of age 18 to 29, and 47% were of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried never-smoker is probably closer, on average, to a never-smoker married to a smoker (an exposed person) than to a never-smoker married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

The proportion of never-smoking controls exposed to spousal smoking varies among studies in the United States. If we exclude studies of uncertain representativeness, the median value for the remaining studies is 0.6. From the evidence on ETS exposure to unmarried female never-smokers, it is reasonable to assume that their exposure to ETS, on average, is at least as large as the average background level plus 60% of the average exposure from spousal smoking. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female never-smokers alike in terms of exposure to ETS (i.e., 60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level only). Consequently, the value $P_2 = 0.6$ is assumed to apply equally to married and unmarried female never-smokers.

The NRC report of 1986 uses $Z = 3$ for the ratio of ETS exposure from spousal smoking plus other sources to ETS exposure from nonspousal sources alone. That value was primarily based on data from Wald and Ritchie (1984), for men in Great Britain, although Lee (1987b) had reported a value of 3.3 for women in Great Britain. The results of Coultas et al. (1987) also were considered, wherein a value of 2.35 was observed for saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. More recent data suggest that a lower value of Z may be more accurate for the United States. The study of 663 volunteers in Buffalo, New York, reported by Cummings et al. (1990), observed a value of 1.55 based on mean urinary cotinine levels among married females ($n = 225$; Cummings, 1990). A study by Wall et al. (1988) containing 48 nonsmokers observed a ratio of mean cotinine levels of 1.53. A survey of municipal workers at a health fair found a cotinine ratio of 2.48 for the 112 women surveyed, but the comparison is between women who shared living quarters with a smoker and those who did not

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(Haley et al., 1989). The 10-country collaborative cotinine study conducted by IARC (Riboli et al., 1990) collected urinary cotinine samples from nonsmoking women in four groups totaling about 100 each--married to a smoker (yes, no) and employed (yes, no)--including two locations, Los Angeles and New Orleans, in the continental United States. The ratios of average cotinine/creatinine concentrations for women married to a smoker to women not married to a smoker range from 1.75 to 1.89 in New Orleans, when the percentage of women employed is assumed to be between 25% and 75%. The data from Los Angeles contain an abnormally high mean for women who are employed and also married to a smoker (a mean of 14.6 based on only 13 observations, compared to the other three means for Los Angeles of 2.1, 4.5, and 6.6), so only the two means for unemployed women (married to a smoker and married to a nonsmoker) were used. The resultant ratio of cotinine/creatinine concentrations is 1.45. Data from the Fontham et al. (1991) study of lung cancer and ETS exposure in five U.S. cities yield a Z of 2.0 based on mean urinary cotinine levels in 239 never-smoking women (data provided by Dr. Elizabeth Fontham).

Cotinine data exhibit variability both within and between subjects, as well as between studies due to different experimental designs, protocols, and geographical locations (see also Chapter 3). Most of the Z values from recent U.S. studies range between 1.55 and 2.0. A value of 1.75 for Z appears reasonable based on the available U.S. data and will be used in Section 6.3.3 along with the combined RR estimate from 11 U.S. studies (Chapter 5) to calculate ETS-attributable lung cancer mortality estimates. Z = 2.0 and Z = 2.6, which are based on *median* cotinine levels, will be used in Section 6.3.4 for alternative calculations of lung cancer mortality based on the results of the Fontham et al. (1991) study. The sensitivity of the lung cancer mortality estimates to changes in Z and other parameters is discussed in Section 6.3.5.

6.3.3. U.S. Lung Cancer Mortality Estimates Based on Results of Combined Estimates from 11 U.S. Studies

This section calculates ETS-attributable U.S. lung cancer mortality estimates based on the combined relative risk estimate (RR_2 = 1.19) derived in Chapter 5 for the 11 U.S. studies. Alternatively, the estimate from just the combined Tier 1 and Tier 2 studies (RR_2 = 1.22 from 8 of the 11; see Table 5-17) could have been used because these eight studies were assessed as having the greater utility in terms of evaluating the lung cancer risks from ETS; however, the results would be virtually the same because the relative risk estimates are so similar. It was therefore decided to use the data from all the U.S. studies for the purposes of the population risk assessment.

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6.3.3.1. *U.S. Lung Cancer Mortality Estimates for Female Never-Smokers*

The parameter values presented in Section 6.3.2 are assumed along with $RR_2 = 1.19$. For $Z = 1.75$, $RR_{02} = 1.59$ (from expression 6-2, denoted hereafter as Ex(6-2); see also Table 6-1). Given those parameter values, the formulae in Section 6.3.2 yield the estimated lung cancer mortality for U.S. women in 1985 by smoking status (ever-smoker, never-smoker exposed to spousal ETS, and never-smoker not exposed to spousal ETS) and source (non-tobacco-smoke-related causes, background ETS in never-smokers, spousal ETS in never-smokers, and ever-smoking), as displayed in Table 6-2. The LCMR from non-tobacco-smoke-related causes ($LCMR_{nt}$) is estimated to be 9.4 per 100,000 and is assumed to apply equally to all persons in the target population, regardless of smoking status. The excess LCMR in never-smokers from exposure to background ETS is 3.2, with an additional 2.4 if exposed to spousal ETS. The excess LCMR in ever-smokers, which includes whatever effect exposure to ETS has on ever-smokers as well as the effect from active smoking, is 120.8.

In rounded figures, 5,470 (14.4%) of the 38,000 LCDs in U.S. women age 35 and over in 1985 are unrelated to smoking (active or passive). The remaining 32,530 LCDs (85.6% of the total) are attributable to tobacco smoke: 31,030 in 25.7 million ever-smokers and 1,500 in 32.3 million never-smokers. These 1,500 ETS-attributable LCDs in never-smokers account for about one-third of all LCDs in female never-smokers. Of the 1,500 LCDs, about 1,030 (69%) are due to background ETS, and 470 (31%) are from spousal ETS. In summary, the total 38,000 LCDs from all causes is due to non-tobacco-smoke-related causes, 5,470 (14.4%), occurring in ever-smokers and never-smokers; ever-smoking, i.e., the effects of past and current active smoking as well as ETS exposure, 31,030 (81.7%), occurring in ever-smokers; and background ETS, 1,030 (2.7%), and spousal ETS, 470 (1.2%), occurring in never-smokers. In other words, ever-smoking causes about 81.7% of the lung cancers in women age 35 and over; exposure to ETS from all sources accounts for some 3.9%; and causes unrelated to tobacco smoke are responsible for the remaining 14.4%. The LCDs in never-smokers attributable to ETS equal about 5% (1,500/31,030) of the total attributable to ever-smoking. Part of the mortality attributed to ever-smoking here, however, is due to ETS exposure in former smokers, to be taken into account in Section 6.3.3.3.

6.3.3.2. *U.S. Lung Cancer Mortality Estimates for Male Never-Smokers*

There are 11 studies worldwide of exposure to ETS and lung cancer in males. The studies and their respective relative risks are AKIB, 1.8; BROW, 2.2; BUFF, 33+ years' exposure, 1.6; CORR, 2.0; HUMB, 4.2; KABA, 1.0; LEE, 1.3; HIRA(Coh), 2.25; HOLE(Coh), 3.5; plus the data in Kabat (1990), 1.2; and Varela (1987, Table 13 scaled down to 50 years of exposure), 1.2. (Data

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Table 6-2. Estimated female lung cancer mortality by attributable sources for United States, 1985, using the pooled relative risk estimate from 11 U.S. studies[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,220 (3.2)	410 (1.1)			
NS	Yes	19.38	1,830 (4.8)	620 (1.6)	470 (1.2)		
ES		25.69	2,420 (6.4)			31,030[5] (81.7)	
Total		58.00	5,470 (14.4)	1,030 (2.7)	470 (1.2)	31,030 (81.7)	38,000

[1]Percentage of grand total (38,000) in parentheses.

[2]The nonblank entries in the table are the product of an individual's attributable risk of lung cancer from non-tobacco-smoke-related causes (expression 6-9 (38,000/58,000,000)), the number at risk in column (1), and the following column-specific multiples: Col. (2) 1
Col. (3) $RR_{03} - 1$
Col. (4) $RR_{02} - RR_{03}$
Col. (5) $RR_{01} - 1$

[3]NS = never-smokers; ES = ever-smokers.

[4]Background sources in the absence of tobacco smoke (i.e., in a zero-ETS environment).

[5]This figure attributes all lung cancer in ever-smokers above the background non-tobacco-smoke-related rate to ever-smoking.

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for BROW, BUFF, and HUMB were supplied via personal communication from Drs. Brownson, Buffler, and Humble.) A weighted average of the passive smoking risk (RR_2) from these 11 studies is about 1.6. For the seven U.S. studies, BROW, BUFF, CORR, HUMB, KABA, Kabat (1990), and Varela (1987), the weighted average RR is about 1.4, but this value is heavily weighted (about 66%) by the Kabat (1990) and Varela (1987) studies, neither of which was used in the analysis of the female data. The combined risk for the five U.S. studies not including Kabat (1990) and Varela (1987) is about 1.8, but they are all small, low-weight studies. In any case, the observed relative risks for males appear to be at least as great as those for females.

When an attempt is made to correct the observed male risks for smoker misclassification, however, using the procedures outlined in Appendix B and the community survey-based misclassification factors for males (1.6% for current regular smokers, 15% for current occasional smokers, and 5.9% for former smokers), it is found that for most of these cohorts, the number of smokers misclassified as never-smokers either exceeds the relatively small number of observed never-smokers or is so great as to drive the corrected relative risk substantially below unity. This implies that the misclassification factors from the community surveys are too high to accurately correct the risks in the epidemiologic studies. Until better misclassification data on males are available, no real sense can be made of the male passive smoking relative risks.

Given the greater stability of the more extensive database on females, it was decided to apply the incremental LCMRs for spousal and nonspousal ETS exposure in female never-smokers to male never-smokers. The incremental LCMRs were used instead of the relative risk estimates because relative risk depends on the background risk of lung cancer (from non-tobacco-related causes) as well as the risk from ETS, and background lung cancer risk may differ between females and males. From Section 6.3.3.1, the LCMR from spousal ETS exposure was 2.4 per 100,000 at risk, and the LCMR from nonspousal ETS exposure was 3.2 per 100,000. The 1985 male population age 35 and over is 48 million (U.S. DHHS, 1989), of whom 27.2% (private communication from Dr. Ronald W. Wilson of the U.S. National Center for Health Statistics), or 13.06 million, were never-smokers. Of these, 24% (Wells, 1988), or 3.13 million, were spousally exposed. Applying the female ETS LCMRs, 3.13 million $\times$ 2.4/100,000 = 80 deaths in males from spousal ETS exposure and 13.06 million $\times$ 3.2/100,000 = 420 deaths from nonspousal exposure, for a total of 500 ETS-attributable LCDs among never-smoking males. These estimates based on female LCMRs are believed to be conservatively low because males generally have higher exposure to background ETS than females. This would lead to lower Z values and subsequently higher estimates of deaths attributable to background (nonspousal) ETS sources. In conclusion, confidence in these estimates for male never-smokers is not as high as those for female never-smokers.

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6.3.3.3. *U.S. Lung Cancer Mortality Estimates for Long-Term (5+ Years) Former Smokers*

Because the risk of lung cancer from active smoking decreases with the number of years since smoking cessation (Section 4.2.2), passive smoking may be a significant source of lung cancer risk in long-term former smokers. There is, however, a scarcity of data on the relative risks of lung cancer for former smokers exposed to ETS. With former smokers, it is unknown how much of the observed lung cancer mortality is attributable to non-tobacco-smoke-related causes, how much is due to ETS exposure, and how much is accounted for by prior smoking. Consequently, neither the observational data on the number of lung cancers in the former smokers nor the relative risk data from never-smoking females are utilized. Instead, long-term former smokers are assumed to have the same LCMR from exposure to ETS as never-smoking females, as was assumed above for never-smoking males. In this manner, the lung cancer risk from ETS exposure can be calculated as an additional risk, supplemental to any remaining risk from previous active smoking. There is some uncertainty in the application of this assumption because the additional risk to long-term former smokers from ETS exposure may not, in fact, be the same as the risk to never-smokers. For example, ETS may have a greater promotional effect on former smokers because of their previous exposures to high concentrations of carcinogens from active smoking.

Female ever-smokers comprise about 44.3%, or 25.7 million, of the total U.S. female population age 35 and over of 58 million. Long-term (5+ years) former smokers comprise about 34% of these ever-smokers (U.S. DHHS, 1990b), or about 8.7 million women. Using a 2.2 concordance factor for former smokers married to ever-smokers versus never-smokers married to never-smokers (see Appendix B), it is estimated that about 77% of the former smokers, or about 6.7 million, would be spousally exposed compared with the 60% for the never-smokers. Thus, based on the LCMRs derived for female never-smokers, the expected number of ETS-attributable LCDs for female long-term former smokers would be 6.7 million × 2.40/100,000 = 160 deaths from spousal exposure and 8.7 million × 3.20/100,000 = 280 deaths from nonspousal exposure, for a total of 440.

Male ever-smokers comprise 72.8% of the U.S. male population, age 35 and over, of 48 million, equal to 35 million; of these, about 43% (derived from data in U.S. DHHS, 1990b, page 60, Table 5), or about 15 million, are 5+ year quitters. Of the never-smoking males, 24% were married to smokers (Section 6.3.3.2). Again using a 2.2 concordance factor for former smokers, it is estimated that 41% of the 15 million former smoking males, or 6.2 million, would be married to ever-smokers. Applying the female never-smoker LCMRs from Section 6.3.3.1, 6.2 million × 2.40/100,000 = 150 deaths from spousal ETS exposure and 15 million × 3.20/100,000 = 480 deaths

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from nonspousal ETS exposure for a total of 630 ETS-attributable LCDs among male long-term former smokers.

Table 6-3 displays the resultant estimates for LCDs attributable to background ETS and spousal ETS by sex for never-smokers and for former smokers who have quit for at least 5 years. The LCMRs for background ETS and spousal ETS, assumed to be independent of smoking status and sex, are the same as derived in Section 6.3.3.1 for female never-smokers (3.2 and 2.4, respectively). Background ETS accounts for about 2,200 (72%) and spousal ETS for 860 (28%) of the total due to ETS. Of the 3,060 ETS-attributable LCDs, about two-thirds are in females (1,930, 63%) and one-third in males (1,130, 37%). More females are estimated to be affected because there are more female than male never-smokers. By smoking status, two-thirds are in never-smokers (2,000, 65%) and one-third in former smokers who have quit for at least 5 years (1,060, 35%).

The numbers shown in Table 6-3 depend, of course, on the parameter values assumed for the calculations. The sensitivity of the totals in Table 6-3 to alternative parameter values is addressed in Section 6.3.5. First, however, tables equivalent to Tables 6-2 and 6-3 are developed based on the FONT study alone for comparison.

6.3.4. U.S. Lung Cancer Mortality Estimates Based on Results of the Fontham et al. (1991) Study (FONT)

The estimate of RR_2 (1.19), the risk of lung cancer to female never-smokers with spousal ETS exposure relative to the risk for female never-smokers without spousal ETS exposure, used in Section 6.3.3, is based on the combined outcomes of the 11 U.S. epidemiologic studies from Chapter 5 (see Table 5-17). In this section, the quantitative population impact assessment is repeated with FONT, the single U.S. study with Tier 1 classification (Section 5.4.4), as the source of the estimates of RR_2 and Z (constructed from urine cotinine measures), with the remaining parameter values left unchanged. While a single study has lower power and larger confidence intervals on the relative risk estimate than can be obtained by combining the various U.S. studies, using the specific data from a single study decreases the uncertainties inherent in combining results from studies that are not fully comparable. **FONT is the only study of passive smoking and lung cancer that collected cotinine measurements, thus providing estimates for RR_2 and Z from a single study population.** The total number of lung cancers attributable to total ETS exposure is particularly sensitive to those two parameters (discussed in Section 6.3.5).

The NCI-funded Fontham et al. study (1991) is a large, well-conducted study designed specifically to investigate lung cancer risks from ETS exposure (see also the critical review in

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Table 6-3. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using 11 U.S. studies (never-smokers and former smokers who have quit 5+ years)[1]

Smoking status[2]	Sex	Exposed to spousal ETS	(1) Number at risk (in millions)	Lung cancer mortality (2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	410		410	1,500 (NS,F)
NS	F	Yes	19.38	620	470	1,090	
NS	M	No	9.93	320		320	500 (NS,M)
NS	M	Yes	3.13	100	80	180	
FS	F	No	2.0	60		60	430 (FS,F)
FS	F	Yes	6.7	210	160	370	
FS	M	No	8.8	280		280	630 (FS,M)
FS	M	Yes	6.2	200	150	350	
Total			69.07	2,200 (71.9)	860 (28.1)	3,060	3,060

[1]Percentage of total ETS-attributable lung cancer deaths (3,060) in parentheses.
[2]NS = never-smokers; FS = former smokers who have quit 5+ years ago.

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Appendix A). It addresses some of the methodological issues that have been of concern in the interpretation of results regarding lung cancer and passive smoking: smoker misclassification, use of surrogate respondents, potential recall bias, histopathology of the lung tumors, and possible confounding by other factors (see also Sections 5.3, 5.4.2, and 5.4.3). Cases and controls were drawn from five major cities across the United States (Atlanta, New Orleans, Houston, Los Angeles, and San Francisco) and, hence, should be fairly representative of the general U.S. population, at least of urban areas with moderate climates. Furthermore, the results of the study are consistent across the five cities.

In spite of the care incorporated into the FONT design to avoid smoker misclassification bias, some might still exist; thus, the adjusted relative risk of 1.29 reported in FONT is "corrected" slightly to 1.28 in this report. The parameter P_2, the proportion of never-smokers exposed to spousal ETS, was assigned the value 0.60 in the preceding section. In FONT, the observed proportion of spousal-exposed controls is 0.60 (0.66) for spousal use of cigarettes only (any type of tobacco) among colon-cancer controls and 0.56 (0.63) in population controls. Consequently, the previous value of 0.60 is retained. Of the 669 FONT population controls, whose current cotinine levels are considered the most representative of typical ETS exposure, there were 59 living with a current smoker and 239 whose spouses never smoked. (The other 371 were nonsmoking women who either no longer lived with a smoking spouse or whose spouse was a former smoker.) The *mean* cotinine level for never-smoking women with spouses who are current smokers ($n = 59$) is 15.90 ± 16.46; the mean level for the other 239 was 7.97 ($\pm$ 11.03). The ratio is 15.90/7.97, giving $Z = 2.0$ (data provided by Dr. Elizabeth Fontham). The median is a measure of central tendency that is less sensitive to extremes, so the ratio of *median* cotinine levels is also considered ($Z = 11.4/4.4 = 2.6$). Results for both values of Z are displayed in Tables 6-4 and 6-5, which correspond to Tables 6-2 and 6-3, respectively, of the previous sections for direct comparison.

The results of Section 6.3.2 are based on $RR_2 = 1.19$ (combined U.S. study results) and $Z = 1.75$ (from studies on cotinine levels). In this section, RR_2 and Z are both increased (RR_2 to 1.28 and Z to 2.0 and 2.6). Correcting $RR_2 = 1.28$ for background ETS exposure yields estimates of $RR_{02} = 1.78$ (i.e., the relative risk from spousal and background ETS) for $Z = 2.0$, and $RR_{02} = 1.55$ for $Z = 2.6$. The relative risk estimate from exposure to background ETS only becomes $RR_{03} = 1.39$ for $Z = 2.0$, and $RR_{03} = 1.21$ for $Z = 2.6$. The change in RR_2, from 1.19 to 1.28, increases the estimated number of LCDs from background and spousal ETS, whereas increasing Z decreases the figure for background ETS and has no effect on the number for spousal ETS (see Tables 6-2 and 6-4). Relative to the total ETS-attributable LCD estimate in the last section

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Table 6-4. Female lung cancer mortality estimates by attributable sources for United States, 1985, using both the relative risk estimates and Z values from the Fontham et al. (1991) study[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,120 (2.9) *1,280 (3.4)*	440 (1.2) *270 (0.7)*			
NS	Yes	19.38	1,680 (4.4) *1,920 (5.1)*	660 (1.7) *410 (1.1)*	660 (1.7) *660 (1.7)*		
ES		25.69	2,230 (5.9) *2,550 (6.7)*			31,220[5] (82.2) *30,900[5] (81.3)*	
Total		58.00	5,030 (13.2) *5,760 (15.2)*	1,100 (2.9) *680 (1.8)*	660 (1.7) *660 (1.7)*	31,220 (82.2) *30,900 (81.3)*	38,000

[1]Percentage of grand total (38,000) in parentheses. Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2]See Table 6-2 for formulae for table entries.
[3]NS = never-smokers; ES = ever-smokers.
[4]Baseline lung cancer mortality in the absence of tobacco smoke (i.e., in a zero-ETS environment).
[5]This figure attributes all lung cancer in ever-smokers above the non-tobacco-smoke-related rate to active smoking.

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Source: https://www.industrydocuments.ucsf.edu/docs/xhhl0000

Table 6-5. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using the Fontham et al. (1991) study (never-smokers and former smokers who have quit 5+ years)[1,2]

Smoking status[3]	Sex	Exposed to spousal ETS	(1) Number at risk (in millions)	Lung cancer mortality (2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	440 *270*		440 *270*	1,760 *1,340* (NS,F)
NS	F	Yes	19.38	660 *410*	660 *660*	1,320 *1,070*	
NS	M	No	9.93	340 *210*		340 *210*	560 *390* (NS,M)
NS	M	Yes	3.13	110 *70*	110 *110*	220 *180*	
FS	F	No	2.0	70 *40*		70 *40*	530 *410* (FS,F)
FS	F	Yes	6.7	230 *140*	230 *230*	460 *370*	
FS	M	No	8.8	300 *190*		300 *190*	720 *530* (FS,M)
FS	M	Yes	6.2	210 *130*	210 *210*	420 *340*	
Total			69.07	2,360 (66.1) *1,460 (54.7)*	1,210 (33.9) *1,210 (45.3)*	3,570 *2,670*	3,570 *2,670*

[1]Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2]Percentage of total ETS-attributable lung cancer deaths (3,570; *2,670*) in parentheses.
[3]NS = never-smokers; FS = former smokers who have quit 5+ years ago.

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(3,060), the net effect is an increase of 12% to 3,570 at Z = 2.0, and a decrease of 13% to 2,670 when Z = 2.6. (FONT is the largest study and therefore the dominant influence in the combined relative risk from the 11 U.S. studies [RR_2 = 1.19], so the outcomes being compared here with those in Section 6.3.3 are not independent. Similarly, the Z-value of 1.75 used with RR_2 = 1.19 in the first analysis is subjectively based on the outcomes of several U.S. cotinine studies, including the FONT cotinine results.) Overall, these two analyses support an estimate in the neighborhood of 3,000 total lung cancer deaths in never-smokers and former smokers (quitters of 5+ years) from exposure to ETS in the United States for 1985.

The 3,000 figure is a composite value from estimates of varying degrees of uncertainty. The confidence for the female never-smoker estimates is highest. The lung cancer estimates for never-smoking females from exposure to spousal ETS (470 to 660; from Tables 6-2 and 6-4) are based on the direct evidence from epidemiologic studies and require the fewest assumptions. Adding in a figure for exposure to background ETS in never-smoking females (680 to 1,100) is subject to the assumptions and other uncertainties attached to the estimate of the parameter Z. The relative risk from ETS exposure, which depends on the risk from background sources of lung cancer as well as the risk from ETS, may differ in females and males. Consequently, the absolute risk (LCMR) in never-smoking females was assumed to apply to never-smoking males, adding 390 to 560 to the total (80 to 110 for spousal ETS and 280 to 450 for background ETS; Tables 6-3 and 6-5). Males, however, are thought to have higher background exposures to ETS than females, so this assumption is likely to underestimate the ETS-attributable lung cancer mortality in males.

The confidence in the estimates for former smokers is less than in those for never-smokers. These estimates also are probably low because they assume that ETS-attributable rates in never-smokers and former smokers are the same. Figures for lung cancer mortality from ETS in former smokers, for the same categories as never-smokers (i.e., females and males, background and spousal ETS), account for an additional 940 to 1,250 (totals of 310 to 440 for spousal ETS and 500 to 810 for background ETS, for both sexes). These figures for former smokers are summed from appropriate entries in Tables 6-3 and 6-5 (Tables 6-2 and 6-4 do not make them explicit; they are accounted for in the entry for lung cancer attributable to ever-smoking).

Finally, there is statistical uncertainty in each of the LCD estimates resulting from sampling variations around all of the parameter estimates that were used in the calculations. It is already apparent that the estimate of total lung cancer mortality attributable to ETS is sensitive to the values of Z and RR_2. Uncertainties associated with the parameter values assumed and the sensitivity of the estimated total ETS-attributable LCDs to various parameter values are examined next.

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6.3.5. Sensitivity to Parameter Values

The estimates for ETS-attributable lung cancer mortality are clearly sensitive to the studies, methodology, and choice of models used, and previous methodologies have been presented in Section 6.2. Even for this current model, however, estimates will vary with different input values. Specifically, the estimates depend on the parameter values assumed for the total number of lung cancer deaths from all sources (T), the population size (N), the proportion of ever-smokers in the population (P_1), the proportion of never-smokers exposed to spousal ETS (P_2), the risk of ever-smokers relative to never-smokers (RR_1), the risk of never-smokers exposed to spousal ETS relative to unexposed never-smokers (RR_2), and the ratio of ETS exposure from spousal smoking and background (i.e., nonspousal) sources to background sources alone (Z).

The effects of changing several of the parameters is readily discernible. A change in T/N produces a proportional change in the same direction for all estimates of attributable mortality. A change in P_1 creates a proportional change in the same direction in all mortality figures for ever-smokers and a change in the opposite direction proportional to $1 - P_1$ in all estimates for never-smokers. The parameter values assumed for these three parameters are from the sources described in the preceding text and are assumed to be acceptably accurate. The value of P_2 is assumed to be 0.6, but values between 0.5 and 0.7 are easily credible. At either of those extremes, there is a 17% change in the lung cancer mortality due to spousal smoking, which only amounts to 80 for the first analysis (Table 6-2) and 100 for the second one (Table 6-4). The impact of changing RR_1, RR_2, or Z on the total lung cancer mortality attributable to ETS from the first analysis is displayed in Table 6-6 for RR_1 from 8 to 11, for RR_2 between 1.04 and 1.35 (extremes of the 90% confidence intervals for the 11 U.S. studies; Table 5-17), and for Z in the range 1.5 to 3.0.

For RR_1 in the interval (8,11), the total lung cancer mortality from ETS ranges from about 2,600 to 3,500, a 14% change in either direction relative to the comparison total of 3,060. The extremes are much greater over the range of values considered for RR_2 (1.04 to 1.35). At the low end, where the excess relative risk from spousal ETS is only 4%, there is a 77% decrease in the total lung cancer mortality to 700. The percentage change is roughly equivalent in the opposite direction when the excess relative risk is at the maximum value 35%, for a total of 5,190. The total is also highly sensitive to the value of Z. A decrease of only 0.25 from the comparison value of $Z = 1.75$ increases the total by 36% to 4,160. A 36% decrease in ETS-attributable mortality occurs at $Z = 2.5$, leaving a corresponding estimate of 1,950. At $Z = 3.0$, the total drops further to 1,680, a 45% decrease.

Varying more than one parameter value simultaneously may have a compounding or canceling effect on the total lung cancer mortality due to ETS. For example, at the following

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Table 6-6. Effect of single parameter changes on lung cancer mortality due to ETS in never-smokers and former smokers who have quit 5+ years

Parameter change		LCM due to ETS: Background[1]	Spousal[2]	Total	Percentage of change[3]
None[4]		2,210	850	3,060	0
Z =	1.50	3,310	850	4,160	+36
	1.75	2,210	850	3,060	0
	2.00	1,660	850	2,510	-18
	2.25	1,320	850	2,170	-29
	2.50	1,100	850	1,950	-36
	2.75	950	850	1,800	-41
	3.00	830	850	1,680	-45
RR_2 =	1.04	510	190	700	-77
	1.05	630	240	870	-72
	1.10	1,220	470	1,690	-45
	1.15	1,780	690	2,470	-19
	1.19	2,210	850	3,060	0
	1.20	2,310	890	3,200	+5
	1.25	2,820	1,080	3,900	+27
	1.30	3,290	1,270	4,560	+49
	1.35	3,750	1,440	5,190	+70
RR_1 =	8.00	2,510	970	3,480	+14
	8.50	2,380	920	3,300	+8
	9.00	2,260	870	3,130	+3
	9.26	2,210	850	3,060	0
	9.50	2,160	830	2,990	-2
	10.00	2,060	800	2,860	-7
	10.50	2,020	780	2,800	-9
	11.00	1,890	730	2,620	-14

[1]69,100,000 at risk.
[2]35,400,000 at risk.
[3]Percentage of change from total shown in boldface (the outcome from Tables 6-2 and 6-3, using the 11 U.S. studies).
[4]Z = 1.75, RR_2 = 1.19, RR_1 = 9.26.

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values of RR_2, the range of percentage changes from the total of 3,060 ETS-attributable lung cancer deaths for values of Z in the interval 1.50 to 3.0 are shown in parentheses: $RR_2 = 1.04$ (-69%, -88%), $RR_2 = 1.15$ (+10%, -56%), $RR_2 = 1.25$ (+73%, -30%), and $RR_2 = 1.35$ (+131%, -7%). The total ETS-attributable LCD estimates range from 380 (at $RR_2 = 1.04$, $Z = 3.0$) to 7,060 (at $RR_2 = 1.35$, $Z = 1.5$). Without considering the additional variability that other parameters might add, it is apparent that the estimated lung cancer mortality from ETS is very sensitive to the parameters RR_2 and Z and that the uncertainty in these parameters alone leaves a fairly wide range of possibilities for the true population risk.

While various extreme values of these parameters can lead to the large range of estimates noted, the extremities of this range are less likely possibilities for the true population risk because the parameters RR_2 and Z are not actually independent and would be expected to co-vary in the same direction, not in the opposite direction as expressed by the extreme values. For example, if the contributions of background to total ETS exposure decrease, Z would increase, and the observable relative risk from spousal exposure, RR_2, would be expected to increase as well. In addition, most of the evidence presented in this report suggests that a narrower range of both RR_2 and Z are appropriate. Thus, while substantially higher or lower values are conceivable, this report concludes that the estimate of approximately 3,000 ETS-attributable LCDs based on the 11 U.S. studies is a reasonable one. Furthermore, this estimate is well corroborated by the estimates of 2,700 and 3,600 calculated by analyzing the FONT data alone, the only study dataset from which estimates of both RR_2 and Z are obtainable.

6.4. SUMMARY AND CONCLUSIONS ON POPULATION RISK

Having concluded in the previous chapter that ETS is causally associated with lung cancer in humans and belongs in EPA Group A of known human carcinogens, this chapter assesses the magnitude of that health impact in the U.S. population. The ubiquity of ETS in a typical individual's living environment results in the respiratory uptake of tobacco smoke to some degree in a very high percentage of the adult population, conservatively upwards of 75% based on the outcome of urinary cotinine/creatinine studies in nonsmokers. Compared with observations on active smokers, body cotinine levels in nonsmokers are low, on the order of a few percent, and there is considerable variability in interindividual metabolism of nicotine to cotinine. Some authors have used the relative cotinine levels in active and passive smokers to estimate the probability of lung cancer in nonsmokers by extrapolating downward on a dose-response curve for active smokers. This "cigarette-equivalents" approach requires several assumptions, e.g., that the dose-response curve used for active smokers is reasonably accurate and low-dose extrapolation of risk for active smokers is credible, that cotinine is proportional (and hence a substitute for)

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whatever is used for "dose" in the dose-response curve, and that the risk calculated in this way applies equally to active and passive smokers with equivalent cotinine measures. The effect of differences in physico-chemical properties of mainstream smoke and sidestream smoke (the principal component of ETS), in lung dosimetry between active and passive smoking, and in exposure patterns (related to concentration and duration of exposure) are not fully understood, but the current state of knowledge casts doubts on the validity of these assumptions.

The remaining approach to population risk extrapolates to the general population from the epidemiologic evidence of increased relative risk of lung cancer in never-smoking women married to smokers. To extrapolate exposure and consequent risk to other sources of ETS exposure, cotinine levels of never-smokers exposed to spousal ETS are compared with those of never-smokers exposed only to other sources of ETS (background), and it is assumed that excess risks of lung cancer from ETS exposures, using cotinine levels as a surrogate measure, are proportional to current ETS exposure levels. (Here, cotinine levels are used to gauge relative levels of *ETS* exposure, not to extrapolate between active and passive smoking as in the "cigarette-equivalents" approach.) The use of current cotinine data to estimate ETS exposure in nonsmokers seems reasonable because cotinine levels correlate quite well with questionnaire response on ETS exposure. However, the total estimate of population risk is sensitive to uncertainty in making these assumptions and variability in the use of cotinine measures.

This report uses the modeling approach based on direct ETS epidemiologic evidence because the assumptions are fewer and more valid than for the "cigarette-equivalents" approach, and the abundance of human data from actual environmental exposures makes this preferred approach feasible. The total number of lung cancer deaths in U.S. females from all causes is partitioned into components attributable to non-tobacco-smoke-related causes (background causes unrelated to active or passive smoking), background ETS (also called nonspousal ETS), spousal ETS, and ever-smoking. Two sets of calculations are made for the U.S. female population age 35 and over in 1985 based on parameter values from national statistics and estimates from the epidemiologic studies on ETS and lung cancer. They differ in the values assumed for two parameters in the formulae for attributable risk: RR_2, the relative risk of lung cancer for never-smokers exposed to spousal smoke, and Z, the ratio of cotinine concentrations in never-smokers exposed to spousal ETS to those exposed to background ETS only. The first analysis uses the pooled estimate of RR_2 from the 11 U.S. studies from Chapter 5, and a subjective value of Z based on the outcomes of independent U.S. cotinine studies ($RR_2 = 1.19$ and $Z = 1.75$). The second analysis uses the estimates of RR_2 and Z from the large, high-quality Fontham et al. study

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(1991), the sole U.S. study that collected cotinine data for its study population (RR_2 = 1.28 with mean Z = 2.0 and with median Z = 2.6).

The estimated lung cancer mortality in never-smoking women from ETS (background and spousal ETS) is 1,500 in the first analysis and 1,760 (1,340) in the second analysis for Z = 2.0 (2.6). When estimates for never-smoking males and former smokers (5+ year quitters) of both sexes are added, the corresponding totals are 3,060 and 3,570 (2,670). All of these figures are based on calculations in which unknown parameter values are replaced with numerical estimates that are subject to uncertainty, and departures in either direction cannot be precluded as unrealistic possibilities for the correct population risks. Nonetheless, because of the large database utilized and the extensive analysis performed, there is a high degree of confidence in the estimates derived for female never-smokers. The figures for male never-smokers and former smokers of both sexes are subject to more uncertainty because more assumptions were necessary for extrapolation from the epidemiologic results. The estimates for male never-smokers, in particular, may be on the low side because males generally are exposed to higher levels of background ETS than females. In summary, our analyses support a total of approximately 3,000 as an estimate for the annual U.S. lung cancer deaths in nonsmokers attributable to ETS exposure.

A quantitative estimate of the variance associated with the 3,000 estimate is not possible without many assumptions, both about the model and the accuracy of the parameters used to derive the population estimates. As exhibited in Table 6-6, we believe the largest variability to be associated with RR_2 and Z. Based on the statistical variations, estimates as low as 400 and as high as 7,000 are possible. However, where specific assumptions were made, we believe that they are generally conservative, and we expect that the actual number may be greater than 3,000.

A feature of variability not addressed in the range presented above is the correlation between RR_2 and Z. The greater the correlation, the smaller will be the expected variance of RR_{02}, resulting in a narrower range of lung cancer estimates. Because only one lung cancer study, FONT, allows RR_2 and Z to be jointly estimated, no assessment of this correlation is possible. However, the two point estimates derived from the FONT data--2,700 and 3,600--provide additional reassurance in the 3,000 estimate.

In conclusion, despite some unavoidable uncertainties, we believe these estimates of ETS-attributable lung cancer mortality to be fairly reliable, if not conservatively low, especially with respect to the male nonsmoker component. First, the weight of evidence that ETS is a human lung carcinogen is very strong. Second, the estimates are based on a large amount of data from various studies of human exposures to actual environmental levels of ETS. They do not suffer from a need to extrapolate from an animal species to humans or from high to low exposures, as is nearly always the case in environmental quantitative health risk assessment. Thus, the confidence in

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these estimates is judged to be medium to high. In summary, the evidence demonstrates that ETS has a very substantial and serious public health impact.

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7. PASSIVE SMOKING AND RESPIRATORY DISORDERS OTHER THAN CANCER

7.1. INTRODUCTION

In 1984, a report of the Surgeon General identified cigarette smoking as the major cause of chronic obstructive lung disease in the United States (U.S. DHHS, 1984). The same report stated that there is conclusive evidence showing that smokers are at increased risk of developing respiratory symptoms such as chronic cough, chronic phlegm production, and wheezing (U.S. DHHS, 1984). More recently, longitudinal studies have demonstrated accelerated decline in lung function in smoking adults (Camilli et al., 1987). In children and adolescents who have recently taken up smoking, several cross-sectional studies have found statistically significant increases in the prevalence of respiratory symptoms (cough, phlegm production, and dyspnea [i.e., shortness of breath]) (Seely et al., 1971; Bewley et al., 1973). Longitudinal studies also have demonstrated that, among young teenagers, functional impairment attributable to smoking may be found after as little as 1 year of smoking 10 or more cigarettes per week (Woolcock et al., 1984).

From a pathophysiologic point of view, smoking is associated with significant structural changes in both the airways and the pulmonary parenchyma (U.S. DHHS, 1984). These changes include hypertrophy and hyperplasia of the upper airway mucus glands, leading to an increase in mucus production, with an accompanying increased prevalence of cough and phlegm. Chronic inflammation of the smaller airways leads to bronchial obstruction. However, airway narrowing also may be due to the destruction of the alveolar walls and the consequent decrease in lung elasticity and development of centrilobular emphysema (Bellofiore et al., 1989). Smoking also may increase mucosal permeability to allergens. This may result in increased total and specific IgE levels (Zetterstrom et al., 1981) and increased blood eosinophil counts (Halonen et al., 1982).

The ascertained consequences of active smoking on respiratory health, and the fact that significant effects have been observed at relatively low-dose exposures, lead to an examination for similar effects with environmental tobacco smoke (ETS). Unlike active smoking, involuntary exposure to ETS (or "passive smoking") affects individuals of all ages, particularly infants and children. An extensive analysis of respiratory effects of ETS in children suggests that the lung of the young child may be particularly susceptible to environmental insults (NRC, 1986). Exposures in early periods of life during which the lung is undergoing significant growth and remodeling may alter the pattern of lung development and increase the risk for both acute and chronic respiratory illnesses.

Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and childhood. One-third of all infants have at least one lower respiratory tract illness (bronchitis, bronchiolitis, croup, or pneumonia) during the first year of life (Wright et al., 1989),

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whereas approximately one-fourth have these same illnesses during the second and third years of life (Gwinn et al., 1991). The high incidence of these potentially severe illnesses has an important consequence from a public health viewpoint: Even small increases in risk due to passive exposure to ETS would considerably increase the absolute number of cases in the first 3 years of life (see Chapter 8). In addition, several studies have shown that lower respiratory tract illnesses occurring early in life are associated with a significantly higher prevalence of asthma and other chronic respiratory diseases and with lower levels of respiratory function later in life (reviewed extensively by Samet and collaborators [1983]).

This chapter reviews and analyzes epidemiologic studies of noncancer respiratory system effects of passive smoking, starting with possible biological mechanisms (Section 7.2). The evidence indicating a relationship between exposure to ETS during childhood and acute respiratory illnesses (Section 7.3), middle ear diseases (Section 7.4), chronic respiratory symptoms (Section 7.5), asthma (Section 7.6), sudden infant death syndrome (Section 7.7), and lung function impairment (Section 7.8) is evaluated. Passive smoking as a risk factor for noncancer respiratory illnesses and lower lung function in adults also is analyzed (Section 7.9). A health hazard assessment and population impact is presented in the next chapter.

7.2. BIOLOGICAL MECHANISMS

7.2.1. Plausibility

It is plausible that passive smoking may produce effects similar to those known to be elicited by active smoking. However, several differences both between active and passive forms of exposure and among the individuals exposed to them need to be considered.

The concentration of smoke components inhaled by subjects exposed to ETS is small compared with that from active smoking. Therefore, effect will be highly dependent on the nature of the dose-response curve (NRC, 1986). It is likely that there is a distribution of susceptibility to the effects of ETS that may depend on, among other factors, age, gender, genetic predisposition, respiratory history, and concomitant exposure to other risk factors for the particular outcome being studied. The ability to ascertain responses to very low concentrations also depends on the reliability and sensitivity of the instruments utilized.

Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (U.S. DHHS, 1986). Passive smokers inhale with tidal breaths and continuously. Therefore, patterns of particle deposition and gas diffusion and absorption differ considerably for these two types of inhalation.

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There are also important differences in the physicochemical properties of ETS and MS (see Chapter 3). These have been extensively reviewed earlier by the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986). ETS is a combination of exhaled MS, sidestream smoke (that is, the aerosol that is emitted from the burning cone between puffs), smoke emitted from the burning side of the cigarette during puffs, and gases that diffuse through the cigarette paper into the environment. This mixture may be modified by reactions that occur in the air before involuntary inhalation. This "aging" process includes volatilization of nicotine, which is present in the particulate phase in MS but is almost exclusively a component of the vapor phase of ETS. Aging of ETS also entails a decrease in the mean diameter of its particles from 0.32 μm to 0.1-0.14 μm, compared to a mean particle diameter for MS of 0.4 μm (NRC, 1986).

Individual and socioeconomic susceptibility may be important determinants of possible effects of ETS on respiratory health. A self-selection process almost certainly occurs among subjects who experiment with cigarettes, whereby those more susceptible to the irritant or sensitizing effects of tobacco smoke either never start or quit smoking (the so-called "healthy smoker" effect). Infants, children, and nonsmoking adults thus may include a disproportionate number of susceptible subjects when compared with smoking adults. In addition, recent studies clearly have shown that, as incidence and prevalence of cigarette smoking has decreased, the socioeconomic characteristics of smokers also have changed. Among smokers, the proportion of subjects of lower educational level has increased in the past 20 years (Pierce et al., 1989). The female-to-male ratio also has increased (Fiore et al., 1989), and this is particularly true for young, poor women, in whom incidence and prevalence of smoking has increased (Williamson et al., 1989). It is thus possible that exposure to ETS may be most prevalent today among precisely those infants and children who are known to be at a high risk of developing respiratory illnesses early in life.

7.2.2. Effects of Exposure In Utero and During the First Months of Life

A factor that may significantly modify the effect of passive smoking (particularly in children) is exposure to tobacco smoke components by the fetus during pregnancy. This type of exposure differs considerably from passive smoking; in fact, the fetus (including its lungs) is exposed to components of tobacco smoke that are absorbed by the mother and that cross the placental barrier, whereas passive smoking directly affects the bronchial mucosa and the alveolus. It is difficult to distinguish between the possible effects of smoking during pregnancy and those of ETS exposure after birth. Some women may quit smoking during pregnancy, only to resume after pregnancy is over. Most mothers who smoke during pregnancy continue smoking after the birth of their child (Wright et al., 1991), and among those who stop smoking after birth, the

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influence on that decision of events occurring shortly after birth (such as respiratory illnesses in their child) cannot be excluded. Recall bias also may influence the results of retrospective studies claiming differential effects on lung function of prenatal and postnatal maternal smoking habits (Yarnell and St. Leger, 1979).

To attempt to circumvent these problems, researchers have studied infant lung function shortly after birth (the youngest group of infants reported was 2 weeks old [Neddenriep et al., 1990]), with the implication that subsequent changes encountered could be attributed mainly to ETS exposure. However, the possibility that even brief exposure to ETS may affect the lungs at a highly susceptible age may not be discarded. Maternal smoking during pregnancy needs to be considered, therefore, as a potential modifier of the effect of passive smoking on respiratory health, particularly in children.

Exposure to compounds present in tobacco smoke may affect the fetal and neonatal lung and alter lung structure much like these same compounds do in smoking adults. Neddenriep and coworkers (1990) studied 31 newborns and reported that those whose mothers smoked during pregnancy had significant increases in specific lung compliance (i.e., lung compliance/lung volume) at 2 weeks of age when compared with infants of nonsmoking mothers. The authors concluded that exposure to tobacco products detrimentally affects the elastic properties of the fetal lung. Although these effects also could be attributed to postnatal exposure to ETS, it is unlikely that such a brief period of postnatal exposure would be responsible for these changes affecting the lung parenchyma (U.S. DHHS, 1986).

There is evidence for similar effects of prenatal lung development in animal models. Collins and associates (1985) exposed pregnant rats to MS during day 5 to day 20 of gestation. They found that pups of exposed rats showed reduced lung volume, reduced number of lung saccules, and reduced length of elastin fibers in the lung interstitium. This apparently resulted in a decrease in lung elasticity: For the same inflation pressure, pups of exposed mothers had significantly higher weight-corrected lung volumes than did pups of unexposed mothers. Vidic and coworkers (1989) exposed female rats for 6 months (including mating and gestation) to MS. They found that lungs of their 15-day-old pups had less parenchymal tissue, less extracellular matrix, less collagen, and less elastin than found in lungs of control animals. This may explain the increased lung compliance observed by Collins et al. (1985) in pups exposed to tobacco smoke products in utero.

Hanrahan and coworkers (1990) reported that infants born to smoking mothers had significantly reduced levels of forced expiratory flows. The researchers studied 80 mother/child pairs and found significant correlations between the cotinine/creatinine ratio in urine specimens obtained during pregnancy in the mother and maximal expiratory flows and tidal volumes at a

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postconceptional age of 50 weeks or younger in their children. The investigators concluded that exposure due to prenatal smoking diminishes infant pulmonary function at birth and, by inference, airway size. These authors also measured maximal flows during tidal breathing in their subjects.. At rather low lung volumes, such as those present during tidal breathing, airway size and maximal flows are both a function of lung elasticity. These results thus may be due to both a specific alteration of the infant's airways and an increased lung compliance in infants whose lungs are small relative to the infant's length.

It also has been suggested that the increased IgE levels observed in adult smokers also may be present in fetuses whose mothers smoke during pregnancy. Magnusson (1986) reported that cord serum levels of IgE and IgD were significantly higher for neonates whose mothers smoked during pregnancy, particularly if the neonates had no parental history of allergic disorders. Cord serum levels of IgD (but not of IgE) were increased for neonates whose fathers smoked, and this effect was independent of maternal smoking. A more recent study on a larger sample (more than 1,000 neonates) failed to find any significant difference in cord serum IgE levels between infants (N = 193) of mothers who smoked during pregnancy and those (N = 881) of mothers who did not (Halonen et al., 1991).

It also has been reported recently that the pulmonary neuroendocrine system may be altered in infants whose mothers smoke during pregnancy. The pulmonary neuroendocrine system, located in the tracheobronchial tree, consists of specialized cells (isolated or in clusters called "neuroepithelial bodies") that are closely related to nerves. In humans, these cells increase in number significantly during intrauterine development, reach a maximum around birth, and then rapidly decline during the first 2 years of life. Their function is not well understood, but the presence of potent growth factors and bronchoconstrictive substances in their granules suggests that they play an important role in growth regulation and airway tone control during this period of lung development (Stahlman and Gray, 1984). Chen and coworkers (1987) reported that maternal smoking during pregnancy increases the size of infant lung neuroepithelial bodies and decreases the amount of core granules present in them. Wang and coworkers (1984) had reported previously that mother mice receiving tap water with nicotine during pregnancy and during lactation had offspring with increased numbers of neuroepithelial bodies at 5 days of age when compared with baby mice whose mothers were not exposed. Baby mice exposed to nicotine only during pregnancy had neuroepithelial bodies of intermediate size with respect to these two groups, whereas those exposed only during lactation had neuroepithelial bodies of normal size. By age 30 days, only baby mice exposed to nicotine during both pregnancy and lactation had neuroepithelial bodies that were larger than those of control animals.

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Activation of the pulmonary neuroendocrine system is not limited to ETS exposure; it is activated by active smoking as well. Aguayo and collaborators (1989) reported that bronchoalveolar lavage fluids obtained from healthy smokers have increased levels of bombesin-like peptides, which are a normal component and a secretion product of human lung neuroendocrine cells (Cutz et al., 1981).

In summary, effects of maternal smoking during pregnancy on the fetus are difficult to distinguish from those elicited by early postnatal exposure to ETS. Animal studies suggest that postnatal exposure to tobacco products enhances the effects of in utero exposure to these same products.

7.2.3. Long-Term Significance of Early Effects on Airway Function

By altering the structural and functional properties of the lung, prenatal exposure to tobacco smoke products and early postnatal exposure to ETS increase the likelihood of more severe complications during viral respiratory infections early in life. Martinez and collaborators (1988a) measured lung function before 6 months of age and before any lower respiratory illness in 124 infants. They found that infants with the lowest levels for various indices of airway size were three to nine times more likely to develop wheezing respiratory illnesses during the first year of life than the rest of the population. The same authors (Martinez et al., 1991) subsequently showed that, in these same infants with lower initial levels of lung function, recurrent wheezing illnesses also were more likely to occur during the first 3 years of life. A similar study performed in Australia (Young et al., 1990) confirmed that infants who present episodes of coughing and wheezing during the first 6 months of life have lower maximal expiratory flows before any such illnesses develop.

The increased likelihood of pulmonary complications during viral respiratory infections in infants of smoking parents has important long-term consequences for the affected individual. There is considerable evidence suggesting that subjects with chronic obstructive lung diseases have a history of childhood respiratory illnesses more often than subjects without such diseases (reviewed by Samet and coworkers [1983]). Burrows and collaborators (1988) found that active smokers without asthma (N = 41) who had a history of respiratory troubles before age 16 years showed significantly steeper declines in FEV_1 (as a percentage of predicted) after the age of 40 than did nonasthmatic smokers without such a history (N = 396). Although these results may have been influenced by recall bias, they suggest that lower respiratory tract illnesses during a period of rapid lung development may damage the lung and increase the susceptibility to potentially harmful environmental stimuli.

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There is no information available on the degree of reversibility of changes induced by exposure to ETS during early life. Longitudinal studies of lung function in older children have shown, however, that diminished levels of lung function are found in children of smoking parents at least until the adolescent years.

7.2.4. Exposure to ETS and Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness consists of an enhanced sensitivity of the airways to pharmacologic or physical stimuli that normally produce no changes or only small decreases in lung function in normal individuals. Subjects with bronchial hyperresponsiveness have significant drops in airway conductance and maximal expiratory flows after inhalation of stimuli such as cold air, hypertonic saline, nebulized distilled water, methacholine, or histamine. Bronchial hyperresponsiveness is regarded as characteristic of asthma (O'Connor et al., 1989) and may precede the development of this disease in children (Hopp et al., 1990). It has also been considered as a predisposing factor for chronic airflow limitation in adult life (O'Connor et al., 1989).

Recent studies of large population samples have shown that active smokers have increased prevalence of bronchial hyperresponsiveness (Woolcock et al., 1987; Sparrow et al., 1987; Burney et al., 1987) when compared with nonsmokers. This relationship seems to be independent of other possible determinants of bronchial hyperresponsiveness (O'Connor et al., 1989). However, one large study of almost 2,000 subjects from a general population sample failed to find a significant relationship between smoking and prevalence of bronchial hyperresponsiveness (Rijcken et al., 1987). The subjects involved in the latter study were younger and were therefore exposed to a smaller average cumulative pack-years of smoking than were the subjects of studies in which a positive relationship was found. This suggests that the relationship may be evident only among individuals with a high cumulative exposure.

Epidemiologic studies have demonstrated that exposure to ETS is associated with an increased prevalence of bronchial hyperresponsiveness in children. Murray and Morrison (1986), in a cross-sectional study, reported that asthmatic children of smoking mothers were four times more likely to show increased responsiveness to histamine than were asthmatic children of nonsmoking mothers. O'Connor and coworkers (1987), in a study of a general population sample, found a significant association between maternal smoking and bronchial hyperresponsiveness (as assessed with eucapnic hyperpnea with subfreezing air) among asthmatic children, but not among nonasthmatic children (Weiss et al., 1985). Martinez and coworkers (1988b) reported a fourfold increase in bronchial responsiveness to carbachol among male children of smoking parents when compared with male children of parents who were both nonsmokers. A smaller (and statistically

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not significant) increase in bronchial responsiveness was reported in girls. These authors also found that the effect of parental smoking was stronger in asthmatic children, and results were still significant after controlling for this factor in a multivariable analysis. Because only a small proportion of mothers in this population smoked during pregnancy, the effect was considered to be associated mainly with exposure to ETS in these children. Lebowitz and Quackenboss (1990) showed that odds of having bronchial reactivity (as assessed by the diurnal variability in maximal expiratory flow rate) were 3.6 times as high among 18 children aged 15 years and younger who lived with persons who smoked more than 20 cigarettes per day than among 62 children of the same age who lived with nonsmokers (95% C.I. = 1.2, 10.6). Children living with smokers of 1 to 20 cigarettes per day had a prevalence of bronchial reactivity that was similar to that of children living with nonsmokers.

Therefore, there is evidence indicating that parental smoking enhances bronchial responsiveness in children. The mechanism for this effect and the possible role of atopy in it are unknown. The doses required to enhance bronchial responsiveness in children exposed to ETS are apparently much lower than those required to elicit similar effects among adult active smokers. A process of self-selection, by which adults who are more sensitive to the effects of tobacco smoke do not start smoking or quit smoking earlier, may explain this finding. Variations in bronchial responsiveness with age also may be involved (Hopp et al., 1985).

Increased bronchial responsiveness may be an important predisposing factor for the development of asthma in childhood (Hopp et al., 1990). Moreover, it has been suggested that bronchial hyperresponsiveness may have effects on the developing respiratory system that predispose to chronic obstructive lung disease in later life (O'Connor et al., 1989). Redline et al. (1989) examined bronchial responsiveness to hyperventilation with cold air and its association with growth of lung function over a 12-year period in 184 children and young adults (aged 8 to 23 years) over a maximum span of 12 years. Among subjects with persistent positive responses to cold air during followup, forced vital capacity grew faster, but forced expiratory flows grew more slowly, than among subjects who consistently did not respond to cold air. Among subjects with intermittently positive cold air responses, forced expiratory flows also grew more slowly than in controls, but growth of forced vital capacity was not changed. Although this study needs confirmation, its results suggest that bronchial hyperresponsiveness may have significant effects on the rate of growth of airway function and lung size in children.

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7.2.5. ETS Exposure and Atopy

Atopy has been defined epidemiologically as the presence of immediate hypersensitivity to at least one potential allergen administered by skin prick test. Atopy is an immediate form of hypersensitivity to antigens (called allergens) that is mediated by IgE immunoglobulin. Allergy (as indicated by positive skin test reactivity to allergens, high levels of circulating IgE, or both) is known to be present in almost all cases of childhood asthma. Recent epidemiologic studies have indicated that an IgE-mediated reaction may be necessary for the occurrence of almost all cases of asthma at any age (Burrows et al., 1989).

Although genetic factors appear to play a major role in the regulation of IgE production (Meyers et al., 1987; Hanson et al., 1991), several reports have indicated that active smoking significantly increases total serum IgE concentrations and may thus influence the occurrence of allergy (Gerrard et al., 1980; Burrows et al., 1981; Zetterstrom et al., 1981; Taylor et al., 1985). Active smokers also have been found to have higher eosinophil counts and increased prevalence of eosinophilia when compared with nonsmokers (Kauffmann et al., 1986; Halonen et al., 1982; Taylor et al., 1985). The physical and chemical similarities between MS and ETS have prompted the investigation of a possible role of passive smoking in allergic sensitization in children.

Weiss and collaborators (1985) first reported a 2.2-fold increased risk of being atopic in children of smoking mothers. Martinez and coworkers (1988b) confirmed that children of smoking parents were significantly more likely to be atopic than were children of nonsmoking parents, and the researchers reported that this association was stronger for male children. They also found a rough dose-response relationship between the number of cigarettes smoked by parents and the intensity of the skin reactions to a battery of allergens. Ronchetti and collaborators (1990) extended these findings in the same population sample of Martinez and coworkers. They found that total serum IgE levels and eosinophil counts were significantly increased in children of smoking parents, and the effect was related to both maternal and paternal smoking.

It is relevant to note that, due to the so-called "healthy smoker effect," children of smokers should be genetically less sensitive than children of nonsmokers, because the latter are likely to include a disproportionate number of allergic subjects who are very sensitive to the irritant effects of smoke. As a consequence, the atopy-inducing effects of ETS may be substantially underestimated.

In summary, there is convincing evidence that both maternal smoking during pregnancy and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization. These changes elicited by exposure to tobacco products may predispose children to lower respiratory tract illnesses early in

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life and to asthma, lower levels of lung function, and chronic airflow limitation later in life. Most of these same effects have been described for active smoking in adults. These smoke-induced changes are, therefore, known biological mechanisms for the increased prevalence of respiratory diseases associated with ETS exposure described later in this chapter.

Exposure to tobacco smoke products during pregnancy and to ETS soon after birth may be the most important preventable cause of early lung and airway damage leading to both lower respiratory illness in early childhood and chronic airflow limitation later in life.

7.3. EFFECT OF PASSIVE SMOKING ON ACUTE RESPIRATORY ILLNESSES IN CHILDREN

A review of the literature that examined the effects of exposure to ETS on the acute respiratory illness experiences of children was contained in the Surgeon General's report on the health consequences of involuntary smoking (U.S. DHHS, 1986) and in the report on environmental tobacco smoke by the NRC (1986). Table 7-1 shows the studies referenced in these two reports.

The Surgeon General's report concluded that "the results of these studies show excess acute respiratory illness in children of parents who smoke, particularly in children under 2 years of age," and that "this pattern is evident in studies conducted with different methodologies and in different locales" (page 44). It estimated that the increased risk of hospitalization for severe bronchitis or pneumonia ranged from 20% to 40% during the first year of life. The report stated that "young children appear to be a more susceptible population for the adverse effects of involuntary smoking than older children and adults" (page 44). Finally, the report suggested that "acute respiratory illnesses during childhood may have long-term effects on lung growth and development, and might increase the susceptibility to the effects of active smoking and to the development of chronic lung disease" (page 44).

The 1986 NRC report observed that "all the studies that have examined the incidence of respiratory illnesses in children under the age of 1 year have shown a positive association between such illnesses and exposure to ETS. The association is very unlikely to have arisen by chance" (page 208). It pointed out that "some of the studies have examined the possibility that the association is indirect by allowing for confounding factors . . . and have concluded that such factors do not explain the results. This argues, therefore, in favor of a causal explanation" (page 208). The report concluded that "bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur up to twice as often during the first year of life in children who have one or more parents who smoke than in children of nonsmokers" (page 217).

Source: https://www.industrydocuments.ucsf.edu/docs/xhhl0000

Table 7-1. Studies on respiratory illness referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Cameron et al. (1969)	158	Children (6 to 9)	X	
Colley (1971)	2,205	Infants	X	
Colley (1974)	1,598	Children (6 to 14)		X
Dutau et al. (1981)	892	Infants/children (0 to 6)		X
Fergusson et al. (1981)	1,265	Infants	X	X
Leeder et al. (1976)	2,149	Infants	X	X
Pedreira et al. (1985)	1,144	Infants	X	X
Pullan and Hey (1982)	130	Children (10 to 11)	X	
Rantakallio (1978)	3,644	Infants/children (0 to 5)	X	X
Speizer et al. (1980)	8,120	Children (6 to 10)	X	X
Ware et al. (1984)	8,528	Children (5 to 9)	X	

7.3.1. Recent Studies on Acute Lower Respiratory Illnesses

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and acute lower respiratory illnesses in children (see Table 7-2).

Chen and coworkers (1986) studied 1,058 infants out of 1,163 infants born in a given period in two neighborhoods in Shanghai, People's Republic of China. Information on hospital admissions from birth to 18 months, smoking habits of household members, parental education, and social and living conditions was obtained by use of a self-administered questionnaire completed by the parents when the child reached 18 months of age. Hospital admissions were divided into those due to respiratory illness and those from all other conditions. None of the mothers in the study smoked. There was no statistically significant association between exposure to ETS and admission to the hospital for any condition other than respiratory illnesses. Compared with nonsmoking households, the risk of being admitted to a hospital for respiratory illnesses was 17% higher when one to nine cigarettes were smoked daily by household members (95% C.I. =

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Table 7-2. Recent epidemiologic studies of effects of passive smoking on acute lower respiratory tract illnesses (LRIs)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Breese-Hall et al. (1984)	Cases: 29 infants hospitalized with bronchiolitis due to respiratory syncytial virus (RSV) Controls: 58 infants hospitalized for nonrespiratory conditions; 58 infants hospitalized due to LRIs not due to RSV	Parental questionnaire	See population studied	Cases vs. controls Odds ratio (OR) = 4.8 (1.8, 13.0) (>5 cig./day vs. none) LRI controls vs. non-LRI controls OR = 2.7 (1.3, 5.7)	Cases matched to controls for age, sex, race, month of admission, form of payment; selection bias not ruled out
Chen et al. (1986)	1,058 infants born in Shanghai, China	Parental self-administered questionnaire; number of cigarettes smoked by household members	Admissions to hospital for respiratory illness as reported by parents	Cig./day OR 1-9 1.2 (0.6, 2.3) >9 1.9 (1.1, 3.4)	Controlling for crowding, paternal education, feeding practices, birthweight, family history of chronic respiratory illness

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Chen et al. (1988)	2,227 infants born in Shanghai, China	Household self-administered questionnaire	Incidence of hospitalization for respiratory illness, incidence of bronchitis or pneumonia first 18 mo. of life	First 6 mo. of life: OR = 3.0 (1.6, 5.7); 7-18 mo. of life: OR = 1.8 (1.0, 3.2)	No smoking mothers; controlling for sex, birthweight, feeding practices, nursery care, paternal education, use of coal for cooking, family history of chronic respiratory illness
Chen (1989)	Same as above	Same as above	Same as above	First 18 mo. of life: incidence density ratio (IDR) = 1.6 for breast-fed babies; IDR = 3.4 for non-breast-fed babies; confidence intervals not calculable	

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986a)	53 infants with bronchiolitis; 106 controls	Parental questionnaire at mean age 8 yr.	See population studied	Cases vs. controls OR = 2.4 (1.2, 4.8) (smoking mother vs. nonsmoking mother)	Cases matched to controls for sex and age; controlling for family history of asthma, social status, older siblings, crowding; selection bias not ruled out
Ogston et al. (1987)	1,565 infants in New Zealand	Maternal and paternal smoking habits during pregnancy by questionnaire	Upper and lower respiratory illnesses during first year of life	Paternal smoking OR = 1.43 (1.05, 1.96); maternal smoking OR = 1.82 (1.25, 3.64)	Upper and lower respiratory illnesses not distinguished; controlling for maternal age, feeding practices, heating type, social class
Anderson et al. (1988)	102 children hospitalized in Atlanta, Georgia, <2 yr.; 199 controls	Self-reported smoking habits of family members	LRI	No effect of parental smoking after controlling for other risk factors	Selection bias possible

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Woodward et al. (1990)	2,125 children aged 18 mo. to 3 yr.	Self-administered mailed questionnaire	"Respiratory score" regarding 13 different symptoms; top 20% compared with low 20%	OR = 2.0 (1.3, 3.4) of having a smoking mother for high scores compared with low scores; no effect of paternal smoking	Controlling for parental history of respiratory illness, child care, parental occupation, maternal stress
Wright et al. (1991)	847 white children born in Tucson, Arizona	Self-administered questionnaire and cotinine levels in a subsample	LRIs as assessed by the infants' pediatricians	OR = 1.5 (1.1, 2.2) of having smoking mother; no effect of paternal smoking	Effects significant only for LRIs occurring in the first 6 mo. of life; controlling for day care, room sharing, parental history of respiratory illnesses, feeding practices, sex, and maternal education
Reese et al. (1992)	491 children aged 1 mo. to 17 yr.	Cotinine levels in urine of children; questionnaire of parents' current smoking	Hospitalization for bronchiolitis	Higher levels in children hospitalized for bronchiolitis than in controls ($p<0.02$)	No effects of ETS on hospitalization for asthma

[1]95% confidence intervals in parentheses.

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Table 5-5. Estimated relative risk of lung cancer from spousal ETS by epidemiologic study (crude and adjusted for cofactors)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
AKIB	1.52 (0.96, 2.41)	1.5 (1.0, 2.5)
BROW	1.52[4] (0.49, 4.79) 1.82[4,5] (0.45, 7.36)[6]	* 1.68[4,5] (0.39, 6.90)[6]
BUFF	0.81[7] (0.39, 1.66)	*
CHAN	0.75[5] (0.48, 1.19)	*
CORR	2.07[8] (0.94, 4.52)	*
FONT[9]	1.37 (1.10, 1.69) 1.21 (0.94, 1.56) 1.32 (1.08, 1.61)	1.29 (1.03, 1.62) 1.28 (0.98, 1.66) *
GAO	1.19 (0.87, 1.63)	1.34[10,11]
GARF	1.31 (0.93, 1.85)	1.70[12] (0.98, 2.94)[6]
GENG	2.16 (1.21, 3.84)	*
HIRA[13]	1.53[10] (1.10, 2.13)	1.64[10] *
HUMB	2.34 (0.96, 5.69)	2.2 (0.9, 5.5)
INOU	2.55[14] (0.90, 7.20)	2.54[10,15] *
JANE	0.86 (0.57, 1.29)	0.93/0.44[16]

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hospitalization. Information on smoking habits in the family was obtained at the time of each patient's admission. Cases were 4.8 times as likely as controls (95% C.I. = 1.8, 13.0) to have one or more household members who smoked five or more cigarettes per day. However, there was no significant difference in the prevalence of cigarette smoking in the households of subjects with respiratory illnesses caused by RSV and those not caused by RSV. This was attributable to the fact that the controls with respiratory illnesses not caused by RSV were also much more likely to live with smokers of five or more cigarettes per day than were controls with nonrespiratory illnesses (OR = 2.7, 95% C.I. = 1.3, 5.7). Little information is given about enrollment and refusals; thus, it is not possible to know if selection bias may have influenced the results. Also, other possible confounders such as socioeconomic level were not taken into account when matching cases to controls or when data were analyzed.

McConnochie and Roghmann (1986a) compared 53 infants drawn from the patient population of a group practice in Rochester, New York, who had physician-diagnosed bronchiolitis before age 2 years, with 106 controls from the same practice who did not have lower respiratory illnesses during the first 2 years of life and who were matched with cases for sex and age. Parental interviews were conducted when the child had a mean age of 8.4 years. Parents were asked about family history of respiratory conditions and allergy, socioeconomic status, passive smoking, home cooking fuel, home heating methods, and household pets. Passive smoking was defined as current and former smoking of "at least 20 packs of cigarettes or 12 ounces of tobacco while living in the home with the subject." Current and former smoking was scored equally, based on the assumption that the report of either reflected passive smoking in the first 2 years of life. Frequency of paternal smoking was not increased among children who had bronchiolitis. Cases were 2.4 times (95% C.I. = 1.2, 4.8) as likely to have smoking mothers as were controls. The association was stronger in families with older siblings (OR = 8.9); however, a multiplicative test for this interaction did not reach statistical significance. The authors studied 63% of eligible cases and 34% of eligible controls. Although the reasons for exclusion from both groups are detailed, selection bias cannot be excluded completely, and the authors give no information about maternal smoking habits among excluded subjects. Also, overreporting of smoking by parents who were aware of their child's history of bronchiolitis may have introduced biases due to differential misclassification. However, the results were consistent across groups classified according to family history of asthma or allergy, social status, presence of older siblings, and crowding.

Ogston and coworkers (1987) conducted a prospective study of 1,565 infants of primigravidae enrolled antenatally in the Tayside Morbidity and Mortality Study in New Zealand. Information on the father's smoking habits and on the mother's smoking habits during pregnancy

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was obtained at the first antenatal interview and from a postnatal questionnaire. A summary record was completed when the child was 1 year of age and included a report of the child's respiratory illnesses (defined as "infections of the upper or lower respiratory tract") during the first year of life derived from observations made by health visitors during scheduled visits to see the child. The authors used a multiple logistic regression to control for the possible effects of maternal age, feeding practices, heating type, and father's social class on the relationship between parental smoking and child health. Of the 588 children of nonsmokers in this sample, 146 (24.8%) had respiratory illnesses during the first year of life. Paternal smoking was associated with a 43% increase (95% C.I. = 4.7, 96.1) in the risk of having respiratory illnesses in the first year of life, and this was independent of maternal smoking. The risk of having a respiratory illness was 82% higher (95% C.I. = 25.6, 264.4) in infants of smoking mothers than in infants of nonsmoking parents. Smoking by both parents did not increase the risk of having respiratory illnesses beyond the level observed in infants with smoking mothers and nonsmoking fathers. It is difficult to compare this study with other reports on the same issue because the authors could not distinguish between upper and lower respiratory tract illnesses.

Anderson and coworkers (1988) performed a case-control study of 102 infants and young children hospitalized in Atlanta, Georgia, for lower respiratory tract illnesses before age 2 and 199 age- and sex-matched controls. The unadjusted relative odds of having any family member smoking cigarettes were 2.0 times as high ($p < 0.05$) among cases as among controls (confidence interval was not calculable from the reported data). The effect disappeared, however, after controlling for other factors (prematurity, history of allergy in the child, feeding practices, number of persons sleeping in the same room with the child, immunization of the child in the last month) in a multivariable logistic regression analysis. No information is provided in this report about maternal and paternal smoking separately, and the number of cigarettes smoked at home by each family member was not recorded either. Also, almost 30% of all target cases declined participation in the study, and no information was available on smoking habits in the families of these children. No information is given about number of refusals among controls.

Woodward and collaborators (1990) obtained information about the history of acute respiratory illnesses in the previous 12 months on 2,125 children aged 18 months to 3 years whose parents answered a questionnaire mailed to 4,985 eligible families in Adelaide, Australia. A "respiratory score" was calculated from responses to questions regarding 13 different upper and lower respiratory illnesses. A total of 1,218 parents (57%) gave further consent for a home interview. From this total, parents of 258 cases (children whose respiratory score fell in the top 20% of scores) and 231 "controls" (children whose scores were within the bottom 20% of scores) were interviewed at home. When compared with controls, cases were twice as likely to have a

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mother who smoked during the first year of life (95% C.I. = 1.3, 3.4). This effect was independent of parental history of respiratory illnesses, other smokers in the home, use of group child care, parental occupation, and level of maternal stress and social support. The authors found no differences in the way smokers and nonsmokers perceived or managed acute respiratory illnesses in their children. Based on this finding, they ruled out that such differences could explain their findings. They also reported that feeding practices strongly modified the effect of maternal smoking; among breast-fed infants, cases were 1.8 times as likely to have smoking mothers as were controls (95% C.I. = 1.2, 2.8), whereas among non-breast-fed infants, cases were 11.5 times as likely to have smoking mothers as were controls (95% C.I. = 3.4, 38.5).

Wright and collaborators (1991) studied the relationship between parental smoking and incidence of lower respiratory tract illnesses in the first year of life in a cohort of 847 white non-Hispanic infants from Tucson, Arizona, who were enrolled at birth and followed prospectively. Lower respiratory illnesses were diagnosed by the infants' pediatricians. Maternal and paternal smoking was ascertained by questionnaire. For verification of smoking habits, the researchers measured cotinine in umbilical cord serum of a sample of 133 newborns who were representative of the population as a whole. Cotinine was detectable in umbilical cord sera of all infants whose mothers reported smoking during pregnancy and in 7 of 100 cord specimens of infants whose mothers said they had not smoked during pregnancy. There was a strong relationship between cotinine level at birth and the amount that the mother reported having smoked during pregnancy.

Children whose fathers smoked were no more likely to have a lower respiratory tract illness in the first year of life than were children of nonsmoking fathers (31.3% vs. 32.2%, respectively). The incidence of lower respiratory tract illnesses was 1.5 times higher (95% C.I. = 1.1, 2.2) in infants whose mothers smoked as in infants whose mothers were nonsmokers. This relationship became stronger when mothers who were heavy smokers were separated from light smokers; 45.0% of children born to mothers who smoked more than 20 cigarettes per day had a lower respiratory illness, compared with 32.1% of children whose mothers smoked 1 to 19 cigarettes per day and 30.5% of children of nonsmoking mothers ($p < 0.05$). The authors tried to differentiate the effects of maternal smoking during pregnancy from those of postnatal exposure to ETS but concluded that the amount smoked contributed more to lower respiratory tract illness rates than did the time of exposure. The authors also found that maternal smoking had a significant effect on the incidence of lower respiratory tract illnesses only for the first 6 months of life; the risk of having a first lower respiratory illness between 6 and 12 months was independent of maternal smoking habits. A logistic regression showed that the effect of maternal smoking was independent of parental childhood respiratory troubles, season of birth, day-care

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use, and room sharing. Feeding practices, maternal education, and child's gender were unrelated to incidence of lower respiratory illnesses in this sample and were not included in the regression. The analysis also showed a significant interaction between maternal smoking and day-care use; the effects of maternal smoking were significant when the child did not use day care (OR = 2.7; 95% C.I. = 1.2, 5.8) but were weaker and did not reach significance among infants who used day care (OR = 1.9; 95% C.I. = 0.9, 4.0). The authors suggested that day-care use may protect against lower respiratory illnesses by reducing exposure to ETS.

Reese et al. (1992) studied urinary cotinine levels in 491 children, aged 1 month to 17 years, on admission to hospital. Children admitted for bronchiolitis had higher urinary cotinine levels than a group of children of similar age admitted for nonrespiratory illnesses ($p < 0.02$). The researchers concluded that there are objective data linking passive smoking to hospital admission for bronchiolitis in infants.

7.3.2. Summary and Discussion on Acute Respiratory Illnesses

Both the literature referenced in the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) and the additional, more recent studies considered in this report provide strong evidence that children who are exposed to ETS in their home environment are at considerably higher risk of having acute lower respiratory tract illnesses than are unexposed children. Increased risk associated with ETS exposure has been found in different locales, using different methodologies, and in both inpatient and outpatient settings. The effects are biologically plausible (see Section 7.2). Several studies also have reported a dose-response relationship between degree of exposure (as measured by number of cigarettes smoked in the household) and risk of acute respiratory illnesses. This also supports the existence of a causal explanation for the association.

The majority of studies found that the effect was stronger among children whose mothers smoked than among those whose fathers smoked. This is further evidence in favor of a causal explanation, because infants are generally in closer and more frequent contact with their mothers. There are now also fairly convincing data showing that the increased incidence of acute respiratory illnesses cannot be attributed exclusively to in utero exposure to maternal smoke. In fact, Chen (1989) and Chen and coworkers (1986, 1988) reported increased risk of acute respiratory illnesses in Chinese children living with smoking fathers and in the total absence of smoking mothers. This effect also could be attributed either to in utero exposure to the father's smoke or to an effect on the father's sperm. This seems unlikely, however, because no such effects of parental smoking during pregnancy have been described in similar studies performed in Western countries. Furthermore, Woodward and coworkers (1990) found that children of smoking mothers were significantly more prone to acute respiratory illnesses even after mothers who

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smoked during pregnancy were excluded from the analysis. This clearly suggests the existence of direct effects of ETS exposure on the young child's respiratory health that are independent of in utero exposure to tobacco smoke products.

There is also convincing evidence that the risk is inversely correlated with age; infants aged 3 months or less are reported to be 3.3 times more likely to have lower respiratory illnesses if their mothers smoke 20 or more cigarettes per day than are infants of nonsmoking mothers (Wright et al., 1991). Increases in incidence of 50% to 100% (relative risks of 1.5-2.0) have been reported in older infants and young children. The evidence for an effect of ETS is less persuasive for school-age children, although trends go in the same direction as those reported for younger children. This may be due to a decrease in illness frequency, to physiological development of the respiratory tract or immune system with age, or to a decreased contact between mother and child with age.

Reasonable attempts have been made in most studies to adjust for a wide spectrum of possible confounders. The analyses indicate that the effects are independent of race, parental respiratory symptoms, presence of other siblings, socioeconomic status or parental education, crowding, maternal age, child's sex, and source of energy for cooking. One study (Graham et al., 1990) also showed that the effect of ETS exposure on proneness to acute respiratory illnesses in infancy and early childhood was also independent of several indices of maternal stress, lack of maternal social support, and family dysfunction. Other factors, such as breastfeeding, decreased birthweight, and day-care attendance, have been shown to modify the risk.

Some sources of bias may have influenced the results, but it is highly unlikely that they explain the consistent association between acute lower respiratory illness and ETS exposure. With one exception (Wright et al., 1991), all studies relied exclusively on questionnaires or interviews to assess exposure. Although questions tend to be very specific, overreporting or more accurate reporting of smoking habits by parents of affected children is possible, particularly in case-control and retrospective studies. However, such a bias should affect both respiratory and nonrespiratory outcomes, and at least two studies have shown no association between nonrespiratory outcomes and ETS exposure (Chen et al., 1988; Breese-Hall et al., 1984). Selection bias could not be excluded in some case-control studies, but satisfactory efforts were made to avoid this source of bias in most studies.

7.4. PASSIVE SMOKING AND ACUTE AND CHRONIC MIDDLE EAR DISEASES

The Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) reviewed five studies demonstrating an excess of chronic middle ear disease in children exposed to parental cigarette smoke (Table 7-3). Both reports conclude that the data are consistent with increased rates of chronic ear infections and middle ear effusions in children exposed to ETS at home.

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Table 7-3. Studies on middle ear diseases referenced in the Surgeon General's report of 1986

Study	No. of subjects	Age of subjects (years)
Said et al. (1978)	3,290	10-20
Iversen et al. (1985)	337	0-7
Kraemer et al. (1983)	76	Young children (unspecified age)
Black (1985)	450	4-9
Pukander et al. (1985)	264	2-3

7.4.1. Recent Studies on Acute and Chronic Middle Ear Diseases

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and middle ear illnesses in children (Table 7-4).

Fleming and coworkers (1987) examined retrospectively risk factors for the acquisition of infections of the upper respiratory tract in 575 children less than 5 years of age. Information on smoking habits and on upper respiratory tract infections and ear infections in the 2 weeks prior to interview was obtained from the children's guardians. The authors reported a 1.7-fold increase ($p = 0.01$) in the risk of having an upper respiratory illness in children of smoking mothers when compared with children of nonsmoking mothers. This effect was independent of feeding practices, family income, crowding, day-care attendance, number of siblings aged less than 5 years, child's age, and race. The authors calculated that 10% of all upper respiratory illnesses in the population were attributable to maternal smoking, a proportion that was comparable with that attributable to day-care attendance. There was no relationship between maternal smoking and frequency of ear infections in this population sample.

Willatt (1986) studied 93 children who were the entire group of children admitted to a Liverpool hospital for tonsillectomy (considered an index of frequent upper respiratory or ear infections) during a 3-month period and 61 age- and sex-matched controls. The median age was 6.9 years (range 1.8-14.9). Parents were asked about the number of sore throats in the previous 3 months and the smoking habits of all members of the household. There was a significant

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Table 7-4. Recent epidemiologic studies of effects of passive smoking on acute and chronic middle ear diseases

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Willatt (1986)	93 children aged 2-15 yr. admitted to hospital for tonsillectomy; 61 age- and sex-matched controls	Questionnaire answered by parents	Tonsillectomy	OR = 2.1 (1.1, 4.0) of having smoking mothers	Controlling for birthweight, sex, age, feeding practices, social class, crowding, sore throats in other household members
Fleming et al. (1987)	575 children <5 yr.	Questionnaire answered by child's guardian	Upper respiratory illnesses (URI) and infections in previous 2 weeks	OR = 1.7 for URI when mother smoked; no effect on ear infection	Controlling for feeding practices, income, crowding, day care, siblings, sex, race
Tainio et al. (1988)	198 Finnish newborns followed from birth to age 2.3 yr.	Questionnaire to parents	Recurrent otitis media as diagnosed by pediatricians	No effects	No distinction between maternal and paternal smoking; small sample

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Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Reed and Lutz (1988)	24 cases of acute otitis media; 25 controls	Questionnaire to parents	Abnormal tympanometry	OR = 4.9 (1.4, 17.2) of having smokers at home	Small sample; selection bias cannot be ruled out
Hinton (1989)	115 children aged 1-12 yr. admitted for grommet insertion; 36 controls aged 2-11 yr. in Great Britain	Questionnaire to parents	Being admitted for grommet insertion	OR = 2.1 (1.0, 4.5) of having smoking parents	No control for confounders; selection bias not ruled out
Teele et al. (1989)	877 children observed for 1 yr.; 698 observed for 3 yr.; 498 observed for 7 yr. in Boston, Massachusetts	Questionnaire to parents	Acute otitis media; number of days with middle ear effusion	13% more acute otitis during first yr. of life; more days with middle ear effusion ($p<0.009$) only during first yr.; no effects after controlling for confounders	No distinction between paternal and maternal smoking; parents smoking 1 cig./day included among smokers
Corbo et al. (1989)	1,615 children aged 6-13 yr. in Abruzzo, Italy	Questionnaire to parents	Child's snoring as reported by parents	OR = 1.8 (1.1, 3.0) for moderate smokers (1-19 cig./day); OR = 1.9 (1.2, 3.1) for heavy smokers (≥20 cig./day)	No distinction between maternal and paternal smoking

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Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Strachan et al. (1989)	736 children in third elementary class in Edinburgh, Scotland	Salivary cotinine level	Prevalence of middle ear effusion as assessed by tympanogram	OR for doubling salivary cotinine = 1.14 (1.03, 1.27)	One-third of cases of middle ear effusion attributable to passive smoking; controlling for sex, housing tenure, social class, crowding, gas cooking, damp walls
Takasaka (1990)	77 children aged 4-8 yr. with otitis media with effusion; 134 controls matched for age and sex in Sendai, Japan	Questionnaire to parents	See population studied	No effect	Low power
Etzel et al. (1992)	132 children from day-care facility aged <3 yr.	Serum cotinine levels	Otitis media with effusion	Incidence density ratio 1.4 (1.2, 1.6) for exposed children; increases significant for ages ≤2 years only	8% of cases attributable to ETS exposure

[1]95% confidence intervals in parentheses.

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relationship ($p < 0.05$) between number of episodes of sore throat and number of cigarettes smoked by the mother. The effect was independent of birthweight, sex, child's age, feeding practices, social class, crowding, and number of sore throats and tonsillectomies in other household members. The relative odds of having a smoking mother were 2.1 times as high (95% C.I. = 1.1, 4.0) in children about to undergo tonsillectomy as in children not undergoing tonsillectomy.

Tainio and coworkers (1988) followed 198 healthy newborns from birth to 2.3 years of age. The investigators recorded physician-diagnosed recurrent otitis media (defined as more than four episodes of otitis media during the first 2 years or more than four episodes during the second year). Parental smoking was more frequent (55%) among the infants with recurrent otitis media than in the comparison group (33%; $p < 0.05$). The authors comment, however, that "parental smoking was not a risk factor for recurrent otitis media," probably because there was no significant relationship between parental smoking and recurrent otitis media using definitions of the latter that differed from the one described above. No distinction was made in this study between the possible effects of maternal and paternal smoking. In addition, the study sample was probably too small to obtain reliable risk calculations.

Reed and Lutz (1988) studied 24 of 70 eligible children who had been seen in a family practice office for acute otitis media during a period of 4 months and 25 of 70 eligible children who had been seen for other reasons. Forty-five of these children had tympanograms performed and had information on household smoke exposure. Prevalence of an abnormal tympanogram (indicating the presence of middle ear effusion) was higher among children exposed to smokers at home (OR = 4.86, 95% C.I. = 1.4, 17.2). Results were independent of feeding practices, history of upper respiratory illness in the past month, low socioeconomic status, sex, age, and attendance at a day-care center. Only a small fraction of eligible subjects were included in this study, and the possibility of selection bias as an explanation for the reported results cannot be ruled out.

Hinton (1989) compared 115 children aged 1 to 12 years (mean = 5 years) admitted to a British hospital for grommet insertion with 36 children aged 2 to 11 years (mean = 6 years) with normal ears who were taken from an orthoptic clinic. Prevalence of smoking was significantly higher in parents of cases than in parents of controls (OR = 2.1, 95% C.I. = 1.0, 4.5). Potential sources of selection bias or selective misclassification cannot be determined from the data reported by the author. No effort was made to control for possible confounders.

Teele and coworkers (1989) studied consecutively enrolled children being followed in two health centers in Boston from shortly after birth until 7 years of age. Acute otitis media and middle ear effusion were diagnosed by the children's pediatricians. Data were analyzed for 877 children observed for at least 1 year, 698 children observed for at least 3 years, and 498 children

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observed until 7 years of age. A history of parental smoking was obtained when each child became 2 years old. A parent was considered a smoker if he or she smoked more than one cigarette per day. The child was considered exposed if either parent was a smoker. The authors reported that the incidence of acute otitis media during the first year of life was 13% higher in children of smoking parents when compared with children of nonsmoking parents ($p < 0.05$), but statistical significance was no longer present after controlling for alleged confounders (site of health care, season of birth, birthweight, socioeconomic status, presence and number of siblings, room sharing, feeding practices, and sibling or parental history of ear infection and allergic diseases). Several of these variables may not have been confounders if they were not related to both parental smoking and incidence of acute otitis media. Controlling for risk factors that are not confounders may result in overcorrection. Parental smoking was not associated with an increased risk for acute otitis media during the first 3 years or 7 years of life. Likewise, parental smoking was associated with a significant increase in the number of days with middle ear effusion, but only during the first year of life ($p < 0.009$), and the effect was no longer present after alleged confounders were controlled for. The authors do not provide information on separate risks for maternal and paternal smoking or on the incidence of acute otitis media and middle ear effusion in children of heavy smokers.

Takasaka (1990) performed a case-control study on 201 children aged 4 to 8 in Sendai, Japan. Sixty-seven subjects had otitis media with effusion, and the remaining 134 children were a control group matched to cases by age, sex, and kindergarten class. The investigators found no significant differences in prevalence of exposure to two or more household cigarette smokers between children with and without otitis media with effusion (no information on either odds ratios or C.I.s was given). The power of this study may have been too low to determine risk factors for middle ear effusions reliably.

Corbo and coworkers (1989) examined 1,615 children aged 6 to 13 years who shared a bedroom with siblings or parents in Abruzzo, Italy. Parents were asked if the child snored and the frequency of snoring. Parents were asked about their own smoking habits; they were considered moderate smokers if the summed total for both parents was fewer than 20 cigarettes per day and heavy smokers if the summed total was 20 or more cigarettes per day. Prevalence of habitual snoring in children increased slightly with the amount of cigarettes smoked by parents; children of heavy smokers were 1.9 times as likely to be habitual snorers as children in nonsmoking households (95% C.I. = 1.2, 3.1), whereas children of moderate smokers were 1.8 times as likely to be habitual snorers as children of nonsmoking parents (95% C.I. = 1.1, 3.0). Habitual snorers were more likely to have had a tonsillectomy, but only if their parents smoked. The authors suggested

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that these results are plausible because adult smokers are also at increased risk of being habitual snorers.

Strachan and collaborators (1989) performed tympanograms and collected saliva for cotinine determinations in 736 children in the third primary class (ages 6½ to 7½ years) in Edinburgh, Scotland. Median of salivary cotinine concentrations was 0.19 ng/mL for 405 subjects living with no smoker, 1.8 ng/mL for 241 subjects living with one smoker, and 4.4 ng/mL for 124 subjects living with two or more smokers. For a given number of smokers in the household, girls had higher cotinine levels than boys, and children living in rented houses (i.e., of lower socioeconomic level) had higher cotinine levels than children living in houses owned by their parents. The authors found a linear relation between the logarithm of the salivary cotinine concentration and the prevalence of middle ear effusion. The authors calculated odds ratios for abnormal tympanometry relative to children with undetectable cotinine concentrations, after adjustment for sex, housing tenure (rented or owned), social class, crowding, gas cooking, and the presence of damp walls. The odds ratio for a doubling of salivary cotinine concentration was 1.14 (95% C.I. = 1.03, 1.27). At a salivary cotinine concentration of 1 ng/mL, the odds ratio of having an abnormal tympanogram was 1.7, whereas an odds ratio of 2.3 was calculated for a cotinine level of 5 ng/mL. At least one-third of all cases of middle ear effusion may have been attributable to passive smoking.

Etzel and coworkers (1992) studied 132 children who attended a day-care facility during the first 3 years of life. The investigators measured serum cotinine levels and considered a level of 2.5 ng/mL or more to be indicative of exposure to tobacco smoke. The 87 children with serum cotinine above this level had a significantly (38%) higher rate of new episodes of otitis media with effusion during the first 3 years of life than the 45 children with lower or undetectable levels (incidence density ratio = 1.4, 95% C.I. = 1.2, 1.6). The authors calculated that 8% of the cases of otitis media with effusion occurring in this population were attributable to exposure to tobacco smoke.

7.4.2. Summary and Discussion of Middle Ear Diseases

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies have failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

Available data provide good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS. Several studies in which no

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significant association was found between ETS exposure and middle ear effusion were not specifically designed to test this relationship, and, therefore, either power was insufficient or assessment of the degree of exposure was inadequate. Also, Iversen and coworkers (1985), who assessed middle ear effusion objectively, suggested that the risk associated with passive smoking increased with age. This may explain the negative results of several studies based on preschool children; the sample sizes of these studies may have been inadequate to test for increased risks of 50% or less, as would be expected in children under 6 years of age. The finding of a log-linear dose-response relationship between salivary cotinine levels and the prevalence of abnormal tympanometry in one study (Strachan et al., 1989) adds to the evidence favoring a causal link. Although not all studies adjusted for possible confounders and selection bias cannot be excluded in the case-control studies reviewed, the evidence as a whole suggests that the association is not likely to be due to chance, bias, or factors related to both ETS exposure and middle ear effusion.

The biological mechanisms explaining the association between ETS exposure and middle ear effusion require further elucidation. Otitis media with effusion is usually attributed to a loss of patency of the eustachian tube, which may be enhanced by upper respiratory infection, impaired mucociliary function, or anatomic factors (Strachan et al., 1989). It is possible that pharyngeal narrowing by adenoidal tissue (and, consequently, eustachian tube dysfunction) may be more common in these children. This is suggested by reports of a higher prevalence of maternal smoking among children about to undergo or who have undergone tonsillectomy and by an increased prevalence of habitual snoring among children of smoking parents. Impaired mucociliary clearance has been demonstrated convincingly in smoking adults (U.S. DHHS, 1984). No data are available on mucociliary transport in children exposed to ETS. However, ETS may affect mucociliary clearance in children as in adults. If this were the case and if normal mucociliary clearance is required for rapid resolution of otitis media, exposure to ETS could result in increased prevalence of chronic middle ear effusion.

The increased prevalence of middle ear effusion attributable to ETS exposure has very important public health consequences. Middle ear effusion is the most common reason for hospitalization of young children for an operation and thus imposes a heavy financial burden to the health care system (Black, 1984). There is also evidence suggesting that hearing loss associated with middle ear effusion may have long-term consequences on linguistic and cognitive development (Maran and Wilson, 1986).

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7.5. EFFECT OF PASSIVE SMOKING ON COUGH, PHLEGM, AND WHEEZING

Studies addressing the effects of passive smoking on frequency of chronic cough, phlegm, and wheezing were reviewed both in the Surgeon General's report (U.S. DHHS, 1986) and in the report by the NRC (1986) (see Table 7-5).

The Surgeon General's report concluded that children whose parents smoke were found to have 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The report noted that the association with parental smoking was not statistically significant for all symptoms in all studies, but added that the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home. The report stated that the results of some studies could have been confounded by the child's own smoking habits, but noted that many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. The report concluded that "chronic cough and phlegm are more frequent in children whose parents smoke compared to nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study" (page 107).

The NRC report concluded that "children of parents who smoke compared with children of parents who do not smoke show increased prevalence of respiratory symptoms, usually cough sputum and wheezing. The odds ratios for the larger studies, adjusted for the presence of parental symptoms, were 1.2-1.8, depending on the symptoms. These findings imply that ETS exposures cause respiratory symptoms in some children" (page 216).

7.5.1. Recent Studies on the Effect of Passive Smoking on Cough, Phlegm, and Wheezing

Several recent studies not considered either in the NRC report (1986) or in the Surgeon General's report (U.S. DHHS, 1986) have addressed the relationship between passive smoking and respiratory symptoms in children (Table 7-6).

McConnochie and Roghmann (1986b) studied 223 of 276 eligible children aged 6 to 10 years without a history of bronchiolitis who were drawn from the patient population of a group practice in Rochester, New York. Information regarding the child's history of wheezing in the previous 2 years, socioeconomic status, family history of respiratory illnesses, and smoking in the household was obtained by questionnaire. Information on breastfeeding was obtained by record checks and interviews. Children whose mothers smoked were more likely to be current wheezers than were children whose mothers did not smoke (OR = 2.2, 95% C.I. = 1.0, 4.8). Neither paternal

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Table 7-5. Studies on chronic respiratory symptoms referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Respiratory symptoms	Surgeon General	NRC
Bland et al. (1978)	3,105	Children/adol. (12-13)	Cough	X	X
Charlton (1984)	15,000	Children/adol. (8-19)	Cough	X	
Colley et al. (1974)	2,426	Children (6-14)	Cough	X	X
Dodge (1982)	628	Children (8-10)	Wheeze, phlegm, cough	X	X
Ekwo et al. (1983)	1,355	Children (6-12)	Cough, wheeze	X	
Kasuga et al. (1979)	1,937	Children (6-11)	Wheeze, asthma	X	
Lebowitz and Burrows (1976)	1,525	Children (<15)	Cough, phlegm, wheeze	X	X
Schenker et al. (1983)	4,071	Children (5-14)	Cough, phlegm, wheeze	X	X
Schilling et al. (1977)	816	Children/adol. (7-16)	Cough, phlegm, wheeze	X	X
Tager et al. (1979)	444	Children/adol. (5-19)	Cough, wheeze		X
Ware et al. (1984)	10,106	Children (6-13)	Cough, wheeze, phlegm		X
Weiss et al. (1980)	650	Children (5-9)	Cough, phlegm, wheeze	X	X

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Table 7-6. Recent epidemiologic studies of effects of passive smoking on cough, phlegm, and wheezing

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986b)	223 children aged 6 to 10 yr. in Rochester, New York	Parental questionnaire	Wheezing in the previous 2 yr.	OR = 2.2 (1.0, 4.8) for maternal smoking; no effect of paternal smoking	Effect disappeared after controlling for confounders; strong interaction between smoking and family history of allergy (OR = 4.5 [1.7, 12.0])
Park and Kim (1986)	3,651 children aged 0 to 14 yr. in South Korea	Questionnaire to household members	Cough in the 3 mo. prior to interview	OR = 2.4 (1.4, 4.3) for families smoking 1 to 14 cig./day; OR = 3.2 (1.9, 5.5) for families smoking ≥15 cig./day	Results only significant among families whose adult members did not have chronic cough

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